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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: DIHYDROXY OPEN-ACID SALT OF SIMVASTATIN

(57) Abstract: The instant invention provides methods and pharmaceutical compositions for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin to a patient in need of such treatment. Methods for making the calcium salt of dihydroxy open acid simvastatin are also provided.

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## TITLE OF THE INVENTION

## DIHYDROXY OPEN-ACID SALT OF SIMVASTATIN

## RELATED APPLICATIONS

5                   This application is a continuation-in-part of attorney docket case no. 20357YPIB having USSN 09/656,109 filed September 6, 2000, which is a continuation-in-part of attorney docket case no. 20357YPIA having USSN 09/651,463 filed August 30, 2000, which is a continuation-in-part of PCT/US2000/02627, filed February 2, 2000, which is a continuation-in-part of USSN 09/264,745, filed March 9, 10                   1999, which is a non-provisional application claiming priority to provisional application SN 60/123247, filed March 8, 1999, all of which are herein incorporated by reference in their entirety.

## FIELD OF THE INVENTION

15                   The instant invention relates to crystalline calcium salt of dihydroxy open acid simvastatin, and its use as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.

## BACKGROUND OF THE INVENTION

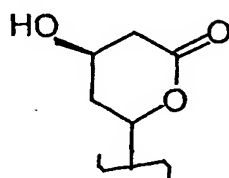
20                   It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease (CHD), and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have 25                   limited efficacy or tolerability, or both. With the introduction of lovastatin (MEVACOR®; see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain comparatively large reductions in plasma cholesterol with very 30                   few adverse effects.

                  In addition to the natural fermentation products, mevastatin and lovastatin, there are now a variety of semi-synthetic and totally synthetic HMG-CoA reductase inhibitors, including simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin 35                   sodium salt (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt

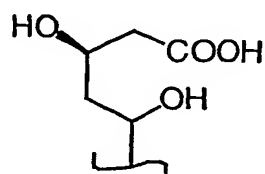
(LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt (also known as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors, are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996).

- 5 The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open-acid, and are often referred to as "statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.

10



Lactone

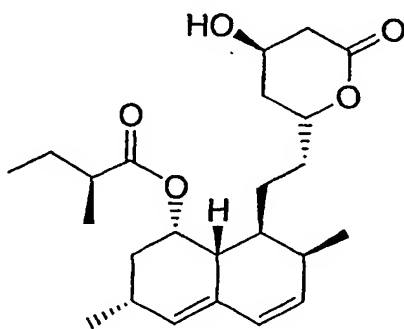


Dihydroxy Open-Acid

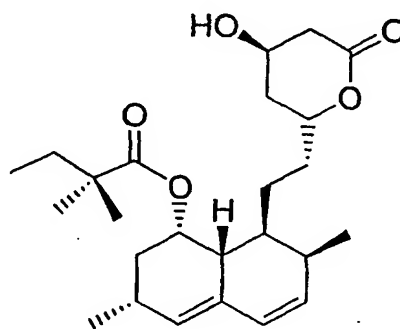
Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms.

Lovastatin and simvastatin are marketed worldwide in their lactonized form.

- 15 Lovastatin is shown as structural formula II, and simvastatin is shown as structural formula III, below.



II



III

- 20 The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that condensation

of the dihydroxy open acid form of statins to the corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under. Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active open acid form, a reaction catalyzed by two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that occurs in blood or in the liver; however, at the pH in blood and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment of the stomach, so that a mixture of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin, and also see A.S. Kearney, et al., Pharmaceutical Research, 1993, 10(10), p. 1461-1465, which describes the interconversion kinetics and equilibrium of CI-981 (atorvastatin in its free acid form). Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug could exist by the time of absorption from the intestine.

The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening step at some point in the process and sometimes formation of a salt at the resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an

alkyl-amide at the resulting carboxy acid, followed by protection of the two hydroxy groups and methylation of the 8'-acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and protection of its hydroxy group. Next, the 8'-position is acylated to introduce the simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8'-acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of all statins, including simvastatin. The mechanism for statin-related myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins. Statins are among the most widely used drugs in the world, and therefore the benefit of any further optimization of their safety profile would be significant.

## SUMMARY OF THE INVENTION

One object of the instant invention is to provide crystalline calcium salt of dihydroxy open acid simvastatin, which includes both hydrated and anhydrous forms of crystalline calcium salt of dihydroxy open acid simvastatin, and particularly the compounds referred to herein as Compounds I, II, III, IV and V.

5 Additional objects are to provide the use of the crystalline forms of the calcium salt of dihydroxy open acid simvastatin, particularly Compounds I to V, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-  
10 release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide processes for making Compounds I to V.

Another object of this invention is to minimize or eliminate the in vivo  
15 lactonization of a dihydroxy open-acid statin. For oral administration, the dihydroxy open-acid statin or a pharmaceutically acceptable salt or ester thereof is to be administered so as to minimize formation of lactonized statin and thereby minimize the amount of lactonized statin that is absorbed from the intestine while maximizing the amount of dihydroxy open-acid statin that is absorbed from the intestine.

## 20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetry (TG) weight loss curve for Compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

Figure 2 is a differential scanning calorimetry (DSC) curve for  
25 Compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

Figure 3 is an x-ray powder diffraction (XRPD) pattern for Compound I. The XRPD pattern was obtained using CuK $\alpha$  radiation. The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta (2 $\theta$ ) in degrees.

30 Figure 4 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum with sideband suppression for Compound I.

Figure 5 is an expanded region from 174-180 parts per million (ppm) of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 4.

35 Figure 6 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum for Compound I.

Figure 7 is an expanded region from 174-180 ppm of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 6.

Figure 8 is a differential scanning calorimetry (DSC) curve for Compound I obtained under a nitrogen flow bubbled through 19.0°C water at a heating rate of 2°C/minute in an open cup.

Figure 9 is an x-ray powder diffraction (XRPD) pattern for Compound I containing all observed XRPD reflections between 2° and 30° 2 theta. The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta (2θ) in degrees.

Figure 10 is an x-ray powder diffraction (XRPD) pattern for Compound II containing all observed XRPD reflections between 2° and 23° 2 theta. The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta (2θ) in degrees.

Figure 11 is a differential scanning calorimetry (DSC) curve for Compound II obtained under a nitrogen flow bubbled through 15.3°C water at a heating rate of 2°C/minute in an open cup.

Figure 12 is a thermogravimetry (TG) weight loss curve for Compound II obtained under a nitrogen flow at a heating rate of 10°C/minute.

Figure 13 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum for Compound II.

Figure 14 is an expanded region from 174-180 ppm of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 13.

Figure 15 is an x-ray powder diffraction (XRPD) pattern for Compound III containing all observed XRPD reflections between 2° and 23° 2 theta. The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta (2θ) in degrees.

Figure 16 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum for Compound III.

Figure 17 is an expanded region from 174-180 ppm of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 13.

Figure 18 is an x-ray powder diffraction (XRPD) pattern for Compound IV containing all observed XRPD reflections between 2° and 23° 2 theta. The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta (2θ) in degrees.

Figure 19 is a differential scanning calorimetry (DSC) curve for Compound IV obtained under a nitrogen flow bubbled through  $-1.0^{\circ}\text{C}$  water at a heating rate of  $2^{\circ}\text{C}/\text{minute}$  in an open cup.

Figure 20 is a thermogravimetry (TG) weight loss curve for Compound IV obtained under a nitrogen flow at a heating rate of  $10^{\circ}\text{C}/\text{minute}$ .

Figure 21 is an x-ray powder diffraction (XRPD) pattern for Compound V containing all observed XRPD reflections between  $2^{\circ}$  and  $23^{\circ}$   $2\theta$ . The ordinate or Y-axis is x-ray intensity (counts) and the abscissa or X-axis is the angle two-theta ( $2\theta$ ) in degrees.

Figure 22 is a differential scanning calorimetry (DSC) curve for Compound V obtained under a nitrogen flow bubbled through  $-1.0^{\circ}\text{C}$  water at a heating rate of  $2^{\circ}\text{C}/\text{minute}$  in an open cup.

Figure 23 is a thermogravimetry (TG) weight loss curve for Compound V obtained under a nitrogen flow at a heating rate of  $10^{\circ}\text{C}/\text{minute}$ .

Figure 24 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum for Compound IV.

Figure 25 is an expanded region from 174-180 ppm of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 24.

Figure 26 is a solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum for Compound V.

Figure 27 is an expanded region from 174-180 ppm of the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 26.

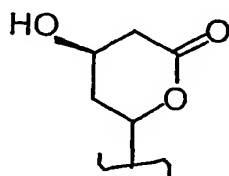
#### DETAILED DESCRIPTION OF THE INVENTION

Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a

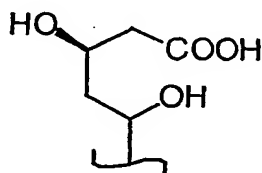
pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway, and also can provide enhanced efficacy. Moreover, maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP3A4 enzymatic pathway.

In addition, novel crystalline forms of the calcium salt of dihydroxy open acid simvastatin have now been discovered to be pharmaceutically suitable salt forms for formulation into an anti-hypercholesterolemic drug composition.

The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".

Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof" are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates and polymorphic crystalline forms are encompassed within the scope of the term "dihydroxy open acid statin(s)."

In the broadest embodiment, any dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof may be used with the present invention. Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof; fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200) and ZD-4522 (see US Patent No. 5,260,440, and Drugs of the Future, 1999, 24(5), pp. 511-513).

In a narrower embodiment, any dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof may be used with the present invention, such as those listed above, provided the statin is not pravastatin or fluvastatin. In a class of this embodiment, the open acid statin includes dihydroxy open acid lovastatin, simvastatin, atorvastatin, cerivastatin, nisvastatin and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts of dihydroxy open acid simvastatin, particularly the ammonium and calcium salts thereof, are preferred for use in the methods and compositions of this invention. More particularly, the calcium salt of dihydroxy open acid simvastatin includes crystalline forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the crystalline forms referred to herein as Compounds I to V.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from

amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C<sub>1-4</sub> alkyl and -C<sub>1-4</sub> alkyl substituted with phenyl-, dimethylamino-, and acetylamino. "C<sub>1-4</sub> alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, *iso*-propyl, *sec*-butyl and *tert*-butyl.

The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP3A4-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway, and also can provide enhanced efficacy. Administering a statin in its open acid form in such a way so as to minimize conversion to its lactonized counterpart, for example by using an oral delayed release dosage form, should reduce the potential for drug interaction compared to the conventional administration of an open acid statin or its lactonized counterpart, for example by using an oral rapid release dosage form.

An object of this invention is to provide methods for reducing the amount of lactonized statin formed and absorbed in the body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release

pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound, i.e., the dihydroxy open-acid statin, until after the dosage form has passed through the stomach.

- 5 Therefore, substantial release of the active compound would initially occur after entry into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active compound in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active compound in the delayed-release dosage form is released in the stomach, i.e., the geometric mean
- 10 ratio of the plasma AUC (area under the curve) of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 90%. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight, i.e., the geometric mean ratio of the plasma AUC of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 95%, and
- 15 more particularly the amount of active compound released in the stomach before entry into the duodenum is 1% or less by weight, i.e., the geometric mean ratio of the plasma AUC of active vs. total HMG-CoA reductase inhibitory activity will be greater than or equal to 99%.

- It is to be understood that metabolism of the dihydroxy open acid
- 20 statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage
- 25 form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

- One example of a suitable delayed-release dosage form is a pH-dependent enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the
- 30 duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example,
- 35 see L. Lachman, The Theory and Practice of Industrial Pharmacy, 3rd Ed., H.

Liebermann and J. Kanig contributors (Lea & Febiger, 1986). An example of a suitable enteric coating includes but is not limited to SURETERIC WHITE® sold by Colorcon which is composed of polyvinyl acetate phthalate, titanium dioxide, talc, colloidal silicon dioxide, triethyl acetate, polyethylene glycol, sodium bicarbonate, purified stearic acid, and sodium alginate. Many other suitable enteric coating materials are commercially available and are known in the art. Additional coatings employed in the preparation of the dosage form, such as those used to provide an elegant, aesthetically pleasing final product or for other purposes, may be applied before or after, or before and after, application of the enteric coating.

Suitable enterically coated pharmaceutical dosage forms for use with this invention include enterically coated conventional rapid-release (also referred to as immediate-release) pharmaceutical dosage forms wherein the drug is relatively rapidly released once the enteric coating is breached, and enterically coated time-controlled release dosage forms such as but not limited to an enterically coated GEM delivery device, described below. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of an enteric coated time controlled-release dosage form is preferred with more potent dosage amounts of a dihydroxy open acid statin so as to lower the systemic exposure to the active statin. Whether the dosage form is an enterically coated rapid-release or time-controlled release dosage form, the enteric coating will prevent release of any substantial amount of the active compound from the dosage form in the stomach.

Enterically coated pharmaceutical dosage forms also include but are not limited to those wherein the dosage form or unit is comprised of the dihydroxy open acid statin in a tablet, capsule or the like that is surrounded by an enteric overcoating, and those wherein the dosage form or unit is a tablet, capsule or the like comprised of enterically coated granules of the dihydroxy open acid statin. Where the dosage form is surrounded by an enteric overcoat, the enteric coating may be the outer-most external coating on the dosage form, or there may be one or more additional finish coatings applied over the enteric coat. In a more limited embodiment, when the delayed-release dosage unit contains enterically coated granules of the drug, the drug is selected from the dihydroxy open-acid form of lovastatin and simvastatin and the pharmaceutically acceptable salt and ester forms thereof, and is more preferably a salt of dihydroxy open acid simvastatin, and most

preferably the calcium or ammonium salt thereof. In an alternative embodiment, any dihydroxy open acid statin or pharmaceutically acceptable salt or ester thereof may be used with the present invention, such as those described herein, provided that the statin is not dosed in a single pharmaceutical dosage form or unit comprised of enteric coated granules of the statin and enteric coated or non-enteric coated granules of aspirin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

(A) a compressed core prepared from an admixture comprising:

- (i) a therapeutically effective amount of the beneficial agent; and
- (ii) a polymer which upon hydration forms gelatinous microscopic particles; and

(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes and the pharmaceutically acceptable salts thereof such as a sodium salt, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P and pharmaceutically acceptable salts thereof, particularly the sodium salt, is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water

insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose. Additional coatings may be applied for aesthetic or functional purposes.

5                   The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate. More preferably, the polymeric coating is comprised of cellulose acetate butyrate and  
10                   triethyl citrate. The GEM device does not function as an osmotic drug delivery device; hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water impermeable" used to describe the polymeric coating define a coating which is  
15                   essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of time the drug is being released from the GEM device in the body. Any minimal  
20                   amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is primarily a function of the number and size of the apertures on the device.

25                   For an elegant, aesthetically pleasing final product, an outer finish coat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically coated, either before or after the application of additional finish coatings. Even without enteric coating, extrusion of the polymer which carries the drug out from inside the compressed core of the GEM  
30                   device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug should not occur in the stomach. Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738. The compound employed with the GEM device may particularly be a pharmaceutically acceptable salt of dihydroxy open acid simvastatin, and more particularly the  
35                   ammonium salt of dihydroxy open acid simvastatin.

The term "patient" includes mammals, especially humans, who use the instant active agents for the prevention or treatment of a medical condition.

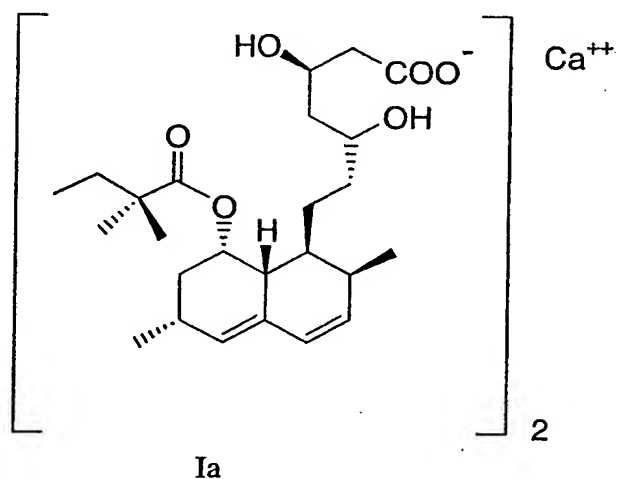
Administering of the drug to the patient includes both self-administration and administration to the patient by another person. The patient may be in need of  
5 treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical  
10 response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical  
15 doctor or other clinician. Particularly, the dosage a patient receives can be selected so as to achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight,  
20 sex and medical condition of the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount  
25 needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are crystalline forms of the calcium salt of dihydroxy open acid simvastatin. One particular crystalline hydrated calcium salt form of dihydroxy open acid simvastatin, herein referred to as Compound I, is the one having an x-ray powder diffraction (XRPD) pattern obtained using CuK $\alpha$   
30 radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. The corresponding XRPD pattern for Compound I is shown in Figure 3.

For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will be

referred to herein as Compound I. Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:



5                   Alternatively, Compound I is also characterized by the XRPD pattern shown in Figure 9. The pattern in Figure 9 was obtained with Cu K $\alpha$  radiation at an accelerating potential of 45 kV and a current of 40 mA from 2° to 30° 2 theta with a step size of 0.015° and a collection time of 1.80 seconds per step. The associated angle 2 theta values and % relative intensity for the XRPD reflections of Compound I with relative intensities of greater than 20% are listed in Table 1. The results in Table 1 are from a compilation of data from three XRPD patterns obtained on the same sample of Compound I which was freshly packed into the x-ray slide for each run employing the same conditions described for obtaining the pattern in Figure 9. These angle 2 theta results were calculated using Philips APD peak search software. The % relative intensity was calculated versus the most intense peak (2 theta = 14.5° - 14.6°) using intensities which were measured with a ruler and recorded as the height of an individual reflection from a hand-drawn baseline. The angle 2 theta results listed in Table 1 are expressed as a range when rounding all three angle 2 theta results from the three trials to the nearest tenths place would not yield the same value for a particular reflection. All other values are expressed as a mean of the three trials.

10

15

20

TABLE 1

Angle (2 theta)	% Relative Intensity
3.6°	25
7.9°	22
10.2 - 10.3°	23 - 28
12.0°	22
13.1 - 13.2°	69 - 73
14.5 - 14.6°	100
14.8 - 14.9°	37 - 45
15.2°	22
17.3 - 17.4°	23 - 31
18.0°	22
19.3°	22
19.7 - 19.8°	32 - 35

- Although Compound I is characterized by the complete group of angle 2 theta values listed in Table 1, all the values are not required for such identification.
- 5 Compound I can be identified by the angle 2 theta value in the range of 17.3 – 17.4°. Compound I can also be identified by any one of the following groups of angle 2 theta values:
- (a) 13.1 – 13.2° and 17.3 – 17.4°;
  - (b) 12.0°, 14.5 – 14.6°, 15.2° and 17.3 – 17.4°;
  - 10 (c) 13.1 – 13.2°, 17.3 – 17.4°, 18.0°, 19.3° and 19.7 – 19.8°;
  - (d) 7.9°, 13.1 – 13.2°, 14.5 – 14.6°, 17.3 – 17.4° and 18.0°; or.
  - (e) 3.6°, 7.9°, 13.1 – 13.2° and 14.5 – 14.6°. Additionally, each of the angle 2 theta values from Table 1 can be expressed to two decimal places as follows: 3.60°, 7.89°, 10.25 - 10.30°, 12.04°, 13.11 - 13.21°, 14.55 - 14.59°, 14.81 - 14.85°, 15.21°, 17.30 - 15 17.42°, 17.97°, 19.28°, 19.75 - 19.78°.

More particularly, each of the angle 2 theta values from Table 1 can be expressed to three decimal places as follows: 3.604°, 7.885°, 10.246 - 10.299°, 12.042°, 13.106 - 13.209°, 14.547 - 14.588°, 14.812 - 14.852°, 15.205°, 17.299 - 17.418°, 17.966°, 19.283°, 19.749 - 19.783°.

In addition to the XRPD patterns described above, Compound I of the instant invention is also characterized by its thermogravimetry (TG) curve. The TG curve of Compound I when obtained under a nitrogen flow at a heating rate of 10°C/minute is characterized by a weight loss in a range from about 6% to about 7%, although a weight loss% outside this range does not rule out the presence of Compound I. For example, Compound I is characterized by the TG curve shown in Figure 1, which was obtained under a nitrogen flow at a heating rate of 10°C/minute and showed a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

Compound I is also characterized by differential scanning calorimetry (DSC), and particularly by either of the DSC curves shown in Figures 2 or 8. When obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, the DSC curve for Compound I is characterized by three lower temperature endotherms with peak temperatures of  $52 \pm 2^\circ$ ,  $77 \pm 2^\circ$  and  $100 \pm 2^\circ$  C, and two higher temperature endotherms due to decomposition with peak temperatures of  $222 \pm 2^\circ$  and  $241 \pm 2^\circ$  C. The DSC curve for Compound I shown in Figure 2 was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is characterized by three lower temperature endotherms with peak temperatures of  $52^\circ$ ,  $77^\circ$  and  $100^\circ$  C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of  $222^\circ$  and  $241^\circ$  C and associated heats of 163 and 92 J/g, respectively.

When obtained on a sample of Compound I in an open cup heated to 220°C at a heating rate of 2°C/min under a nitrogen flow bubbled through water at 19.0°C, the DSC curve for Compound I is characterized by an endotherm with an onset temperature of  $46 \pm 2^\circ$  C and a peak temperature of  $50 \pm 2^\circ$  C, followed by an endotherm with an onset temperature of  $66 \pm 2^\circ$  C and a peak temperature of  $73 \pm 2^\circ$  C, followed by an endotherm with an onset temperature of  $89 \pm 2^\circ$  C and a peak temperature of  $98 \pm 2^\circ$  C, followed by an endotherm due to decomposition with an onset temperature of  $190 \pm 2^\circ$  C and a peak temperature of  $201 \pm 2^\circ$  C. More particularly, the DSC curve for Compound I shown in Figure 8 was obtained on a sample of Compound I in an open cup heated to 220°C at a heating rate of 2°C/min under a nitrogen flow bubbled through water at 19.0°C and is characterized by an endotherm with an onset temperature of  $46^\circ$  C, a peak temperature of  $50^\circ$  C and an

associated heat of 38 J/g, followed by an endotherm with an onset temperature of 66 °C, a peak temperature of 73 °C and an associated heat of 60 J/g, followed by an endotherm with an onset temperature of 89 °C, a peak temperature of 98 °C and an associated heat of 10 J/g, followed by an endotherm due to decomposition with an onset temperature of 190 °C, a peak temperature of 201 °C and an associated heat of 68 J/g.

Compound I is also characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 4, which was completed using a Bruker DSX 400WB NMR system operating at 100.6 MHz for  $^{13}\text{C}$  and 400.1 MHz for  $^1\text{H}$  using a Bruker MAS 400WB BL7 double-resonance probe with a spinning module housing a 7 mm zirconia rotor with Kel-f end caps. The solid-state  $^{13}\text{C}$  nuclear magnetic resonance (NMR) spectrum was acquired using cross polarization (CP), magic-angle spinning (MAS), and high-power (~59 kHz) decoupling with variable-amplitude cross-polarization and total sideband suppression. Proton and carbon  $90^\circ$  pulse widths were 4.25  $\mu\text{sec}$  with a contact time of 2.0 msec. The sample was spun at 7.0 kHz and a total of 1024 scans were collected for the spectrum with a recycle delay of 3.0 seconds. A line broadening of 10 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 ppm) as a secondary reference.

More particularly, when employing the experimental conditions described above for obtaining the solid-state  $^{13}\text{C}$  NMR spectrum of Figure 4, Compound I is characterized by the chemical shift values listed in Table 2 which are present in the 174-180 ppm region of the spectrum.

TABLE 2	
<u>Assignment</u>	<u>Chemical Shift, ppm</u>
Carbonyl Carbon	179.4
	179.0 (broad)
	178.3
	177.9 (broad)
	177.0
	176.7
	176.0
	175.1

Alternatively, Compound I is characterized by solid state  $^{13}\text{C}$  NMR having a chemical shift difference of 0.9 or 3.2 between the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance. Compound I is also characterized by solid state  $^{13}\text{C}$  NMR having chemical shift differences of 0.9, 1.6, 1.9, 2.8, 3.2, 3.9 and 4.3 between the lowest ppm carbonyl carbon resonance and other carbonyl carbon resonances

An expanded view of the relevant region of the Figure 4  $^{13}\text{C}$  NMR spectrum from 174-180 ppm that characterizes Compound I is shown in Figure 5.

Alternatively, Compound I is characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 6, which was obtained using slightly modified experimental conditions than those used to obtain the spectrum of Figure 4. The spectrum of Figure 6 was completed using a Bruker DSX 400WB NMR system operating at 100.6 MHz for  $^{13}\text{C}$  and 400.1 MHz for  $^1\text{H}$  using a Bruker MAS 400WB BL7 double-resonance probe with a spinning module housing a 7 mm zirconia rotor with Kel-f end caps and liquid seal plug. The solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum was acquired using cross polarization (CP), magic-angle spinning (MAS), and high-power (~59 kHz) decoupling with variable-amplitude cross-polarization. Proton  $90^\circ$  pulse width was 4.0  $\mu\text{sec}$ , while carbon  $90^\circ$  pulse width was 4.8  $\mu\text{sec}$  with a contact time of 2.0 msec. The sample was spun at 7.0 kHz and a total of 1024 scans were collected for the spectrum with a recycle delay of 3.0 seconds. A line broadening of 10 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 ppm) as a secondary reference.

More particularly, when employing the experimental conditions described above for obtaining the solid-state  $^{13}\text{C}$  NMR spectrum of Figure 6, Compound I is characterized by the chemical shift values listed in Table 2, above, which are present in the 174-180 ppm region of the spectrum. An expanded view of the relevant region of the Figure 6  $^{13}\text{C}$  NMR spectrum from 174-180 ppm that characterizes Compound I is shown in Figure 7.

Compound I of the instant invention is still further characterized by the  $^1\text{H}$  NMR spectral data,  $^{13}\text{C}$  NMR and mass spectral (MS) data as given in Example 1 herein.

While not wishing to be held to any particular theory, it is believed, based on TG and DSC data of Compound I that Compound I is a hydrated crystalline

form of Compound Ia containing from 2.8 to 3.6 moles of water of hydration per mole of calcium.

It has now further been discovered that compound Ia can exist in several different crystalline forms, each having a different degree of hydration, in addition to the particular hydrated crystalline form associated with Compound I. Each of these additional novel and distinct crystalline forms of the calcium salt of dihydroxy open acid simvastatin, referred to herein as Compounds II, III, IV and V, is characterized by its own unique physical properties.

The XRPD pattern data described below for Compounds II – V was obtained with Cu K $\alpha$  radiation at an accelerating potential of 45 kV and a current of 40 mA from 2° to 23° 2 theta with a step size of 0.015° and a collection time of 1.80 seconds per step. The solid state  $^{13}\text{C}$  NMR data described below for Compounds II – V was obtained using the same experimental procedure described above for obtaining the solid state  $^{13}\text{C}$  NMR spectrum for Compound I shown in Figure 6

The hydrated crystalline form of dihydroxy open acid simvastatin referred to herein as Compound II is characterized by the XRPD pattern shown in Figure 10. This XRPD pattern of Compound II is characterized by reflections with d-spacings at 23.5, 11.0, 8.62, 7.27, 6.55, 6.27, 6.05, 4.99, 4.86 and 4.43Å. The associated angle 2 theta values and % relative intensity for the XRPD reflections of Compound II with relative intensities of greater than 20% are listed in Table 3.

Table 3

<u>Angle ( 2 theta)</u>	<u>% Relative Intensity</u>
3.8°	52
8.1°	21
10.3°	54
12.2°	28
13.5°	74
14.1°	42
14.6°	100
17.8°	36
18.2°	37
20.0°	34

Although Compound II is characterized by the complete group of angle 2 theta values listed in Table 3, all the values are not required for such identification. Compound II can be identified by the following characteristic angle 2 theta values: 12.2 and 13.5°.

5                    Additionally, each of the angle 2 theta values from Table 3 can be expressed to two decimal places as follows: 3.75, 8.06, 10.26, 12.17, 13.50, 14.12, 14.62, 17.77, 18.24 and 20.01°.

                    More particularly, each of the angle 2 theta values from Table 3 can be expressed to three decimal places as follows: 3.754, 8.059, 10.258, 12.165, 13.503,  
10    14.118, 14.623, 17.767, 18.236 and 20.007°.

                    Compound II is also characterized by differential scanning calorimetry, and particularly the DSC curve shown in Figure 11. When obtained at a heating rate of 2°C/minute under a flow of nitrogen bubbled through 15.3°C water on a sample of Compound II in an open cup heated up to 110°C, the DSC curve for Compound II is  
15    characterized by an endotherm with an extrapolated onset temperature of 63 ±2°C and a peak temperature of 70 ±2°C, followed by a second endotherm with an extrapolated onset temperature of 87 ±2°C and a peak temperature of 97 ±2°. For example, the DSC curve for Compound II shown in Figure 11 was obtained at a heating rate of 2°C/minute under a flow of nitrogen bubbled through 15.3°C water on a sample of  
20    Compound II in an open cup heated up to 110°C, and shows an endotherm with an extrapolated onset temperature of 63°C, a peak temperature of 70°C and an associated heat of 68 J/g, followed by a second endotherm with an extrapolated onset temperature of 87°C, a peak temperature of 97°C and an associated heat of 13J/g.

                    Compound II is also characterized by its thermogravimetry curve. For  
25    example, Compound II is characterized by the TG curve shown in Figure 12, which was obtained at a heating rate of 10°C/minute under a flow of nitrogen and shows a 1.5% weight loss up to an inflection point in the weight loss curve at about 50°C, followed by a 4.2% step-wise weight loss between 50°C and a stable weight loss plateau at about 119°C.

30                    Compound II is also characterized by the solid-state <sup>13</sup>C NMR spectrum shown in Figure 13. More particularly, Compound II is characterized by the chemical shift values listed in Table 4 which are present in the 174-180 ppm region of the solid-state <sup>13</sup>C NMR spectrum.

TABLE 4	
<u>Assignment</u>	<u>Chemical Shift</u>
Carbonyl Carbon	179.2 (broad)
	178.0 (broad)
	176.6 (broad)
	176.0 (broad)
	175.6 (broad)
	175.2 (broad)

Compound II can also be characterized by solid state  $^{13}\text{C}$  NMR having a chemical shift difference between the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance of 0.4 or 4.0. Alternatively, compound II can be  
5 characterized by solid state  $^{13}\text{C}$  NMR having a chemical shift difference between the lowest ppm carbonyl carbon resonance and other carbonyl carbon resonances of 0.4, 0.8, 1.4, 2.8 and 4.0.

An expanded view of the relevant region of the Figure 13 spectrum from 174-180 ppm that characterizes compound II is shown in Figure 14.

10 The hydrated crystalline form of dihydroxy open acid simvastatin referred to herein as Compound III is characterized by the XRPD pattern shown in Figure 15. The XRPD pattern of Compound III is characterized by reflections with d-spacings at 9.77, 8.61, 7.51, 6.84, 6.72, 6.25, 5.96, 5.30, 5.24, 4.97, 4.64, 4.58, 4.50 and 4.33 Å. The associated angle 2 theta values and % relative intensity for the XRPD  
15 reflections of Compound III with relative intensities of greater than 20% are listed in Table 5.

Table 5

<u>Angle ( 2 theta)</u>	<u>% Relative Intensity</u>
9.0°	22
10.3°	22
11.8°	28
12.9°	33
13.2°	62
14.1°	100
14.9°	41
16.7°	29
16.9°	28
17.8°	57
19.1°	23
19.4°	51
19.7°	33
20.5°	23

Although Compound III is characterized by the complete group of angle 2 theta values listed in Table 5, all the values are not required for such identification. Compound III can be identified by the following characteristic angle 2  
5 theta values: 9.0 and 11.8°.

Additionally, each of the angle 2 theta values from Table 5 can be expressed to two decimal places as follows: 9.04, 10.26, 11.78, 12.93, 13.16, 14.15, 14.86, 16.71, 16.91, 17.83, 19.09, 19.38, 19.70 and 20.48°.

More particularly, each of the angle 2 theta values from Table 5 can be  
10 expressed to three decimal places as follows: 9.042, 10.263, 11.779, 12.934, 13.159, 14.148, 14.860, 16.713, 16.912, 17.828, 19.093, 19.377, 19.701 and 20.476°.

Compound III is also characterized by the solid-state  $^{13}\text{C}$  NMR spectrum shown in Figure 16. More particularly, Compound III is characterized by the chemical shift values listed in Table 6 which are present in the 174-180 ppm  
15 region of the solid-state  $^{13}\text{C}$  NMR spectrum.

TABLE 6	
<u>Assignment</u> Carbonyl Carbon	<u>Chemical Shift</u>
	178.7
	178.3
	178.1
	177.7
	176.8 (broad)
	176.2
	175.2

Compound III can also be characterized by solid state  $^{13}\text{C}$  NMR having a chemical shift difference between the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance of 1.0 or 3.5. Alternatively, compound III can be characterized by solid state  $^{13}\text{C}$  NMR having a chemical shift difference between the lowest ppm carbonyl carbon resonance and other carbonyl carbon resonances of 1.0, 1.6, 2.5, 2.9, 3.1 and 3.5.

An expanded view of the relevant region of the Figure 16 spectrum from 174-180 ppm that characterizes compound III is shown in Figure 17.

The hydrated crystalline form of dihydroxy open acid simvastatin referred to herein as Compound IV is characterized by the XRPD pattern shown in Figure 18. The XRPD pattern of Compound IV is characterized by reflections with d-spacings at 30.9, 24.2, 13.2, 12.1, 8.69, 6.59 and 6.07 Å. The associated angle 2 theta values and % relative intensity for the XRPD reflections of Compound II with relative intensities of greater than 10% are listed in Table 7.

Table 7

<u>Angle ( 2 theta)</u>	<u>% Relative Intensity</u>
2.9°	21
3.6°	100
6.7°	13
7.3°	13
10.2°	65
13.4°	39
14.6°	37

Although Compound IV is characterized by the complete group of angle 2 theta values listed in Table 7, all the values are not required for such identification. Compound IV can be identified by the following characteristic angle 2 theta values: 6.7 and 13.4°.

5                    Additionally, each of the angle 2 theta values from Table 7 can be expressed to two decimal places as follows: 2.86, 3.65, 6.69, 7.29, 10.17, 13.42 and 14.57°.

                    More particularly, each of the angle 2 theta values from Table 7 can be expressed to three decimal places as follows: 2.857, 3.645, 6.693, 7.285, 10.174,  
10    13.424 and 14.572°.

                    Compound IV is also characterized by differential scanning calorimetry, and particularly the DSC curve shown in Figure 19. When obtained at a heating rate of 2°C/minute under a flow of nitrogen bubbled through -1.0°C water on a sample of Compound IV in an open cup heated up to 110°C, the DSC curve for  
15    Compound IV is characterized by a single endotherm with an extrapolated onset temperature of 76 ±2°C and a peak temperature of 89 ±2°C. °. For example, the DSC curve for Compound IV shown in Figure 19 was obtained at a heating rate of 2°C/minute under a flow of nitrogen bubbled through -1.0°C water on a sample of Compound IV in an open cup heated up to 110°C and shows a single endotherm with  
20    an extrapolated onset temperature of 76°C, a peak temperature of 89°C and an associated heat of 15 J/g.

                    Compound IV is also characterized by its thermogravimetry curve. For example, Compound IV is characterized by the TG curve shown in Figure 20, which was obtained at a heating rate of 10°C/minute under a flow of nitrogen and shows a  
25    1.2% weight loss up to an inflection point in the weight loss curve at about 47°C followed by a 0.7% step-wise weight loss between 47°C and a stable weight loss plateau at about 100°C.

                    Compound IV is also characterized by the solid-state <sup>13</sup>C NMR spectrum shown in Figure 24. More particularly, Compound IV is characterized by  
30    the region from 174-180 ppm of this spectrum. An expanded view of the relevant region of the Figure 24 spectrum from 174-180 ppm that characterizes compound IV is shown in Figure 25.

The crystalline form of dihydroxy open acid simvastatin referred to herein as Compound V is characterized by the XRPD pattern shown in Figure 21. This XRPD pattern of Compound V is characterized by reflections with d-spacings at 28.2, 24.4, 13.5 and 12.2Å. The associated angle 2 theta values and % relative intensity for the XRPD reflections of Compound V with relative intensities of greater than 10% are listed in Table 8.

Table 8

<u>Angle ( 2 theta)</u>	<u>% Relative Intensity</u>
3.1°	34
3.6°	100
6.5°	11
7.2°	11

Although Compound V is characterized by the complete group of angle 2 theta values listed in Table 8, all the values are not required for such identification. Compound V can be identified by the following characteristic angle 2 theta values: 3.1 and 3.6°.

Additionally, each of the angle 2 theta values from Table 8 can be expressed to two decimal places as follows: 3.13, 3.62, 6.52 and 7.24°.

More particularly, each of the angle 2 theta values from Table 8 can be expressed to three decimal places as follows: 3.127, 3.620, 6.522 and 7.242°.

Compound V is also characterized by differential scanning calorimetry, and particularly the DSC curve shown in Figure 22. When obtained at a heating rate of 2°C/minute under a flow of nitrogen bubbled through -1.0°C water on a sample of Compound V in an open cup heated up to 110°C, the DSC curve of Compound V is characterized by showing essentially no observable major thermal event up to a final analysis temperature of about 120°C.

Compound V is also characterized by its thermogravimetry curve. For example, Compound V is characterized by the TG curve shown in Figure 23, which was obtained at a heating rate of 10°C/minute under a flow of nitrogen and shows a 2.5% weight loss up to a stable weight loss plateau at about 92°C.

Compound V is also characterized by the solid-state <sup>13</sup>C NMR spectrum shown in Figure 26. More particularly, Compound V is characterized by the

region from 174-180 ppm of this spectrum. An expanded view of the relevant region of the Figure 26 spectrum from 174-180 ppm that characterizes compound V is shown in Figure 27.

Furthermore, Compounds I, II, III, IV and V are all characterized by having XRPD angle 2 theta reflections in a range from 3.5 to 3.8° 2 theta when employing the experimental conditions described above for obtaining XRPD patterns for Compounds II – V.

Additionally, Compounds I, II, III, IV and V are all characterized by DSC as showing endotherms with peak temperatures of 222  $\pm$ 2°C and 241  $\pm$ 2°C when employing the experimental conditions used to obtain the DSC curve in Figure 2. Similarly, Compounds I, II, III, IV and V are all characterized by DSC as showing an endotherm with a peak temperature of 201  $\pm$ 2°C when employing the experimental conditions used to obtain the DSC curve in Figure 8.

When an X-ray powder diffraction pattern is obtained for a crystalline form of the calcium salt of dihydroxy open acid simvastatin in the presence of other chemical components, including likely pharmaceutical excipients or where mixtures of different crystalline forms exist, it is understood and recognized by one of ordinary skill in the art that the entire diffraction pattern may be shifted and it is within the purview of one of ordinary skill in the art to correct the shift to obtain the spectra described *supra*.

The term “cup” used above is also commonly referred to in the art as a “pan,” and the two terms are interchangeable when describing the DSC experimental procedure. The heats associated with the DSC endotherms described above are examples of results obtained using the indicated experimental conditions, but the heat values are not necessary to characterize the different crystalline salt forms of the calcium salt of dihydroxy open acid simvastatin. When a TG or DSC curve is obtained for any of the crystalline calcium salt compounds herein in the presence of other chemical components, including likely pharmaceutical excipients or where mixtures of different crystalline forms exist, it is understood and recognized by one of ordinary skill in the art that the entire curve may be shifted, and it is within the purview of one of ordinary skill in the art to identify the shape of the curve as characteristic of Compound I, II, IV or V, as appropriate, even if a shift has occurred.

In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the

compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin such as an ammonium salt or calcium salt, and particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as

- 5 Compounds I to V or mixtures thereof. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

#### BOOKMARK

- The instant invention provides methods for inhibiting HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and combined hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal, including a human, who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

- Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

- A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular

events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for  
5 preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event. The patient may or may not have atherosclerotic disease at the time of administration, or may be at risk for developing it.

10 The instant invention also provides a method for preventing and/or treating inflammatory diseases or disorders alone or in conjunction with the treatment of conditions described above, comprising the administration of a dihydroxy open-acid statin to a patient in need of such treatment. This includes, for example, the treatment of inflammatory conditions susceptible to treatment with a non-steroidal  
15 anti-inflammatory agent, arthritis including rheumatoid arthritis, and degenerative joint diseases (osteoarthritis), dementia, Alzheimer's disease, multiple sclerosis, inflammatory bowel disease, asthma, psoriasis, systemic lupus erythematosus, vasculitis, gout, adrenoleukodystrophy, diabetic retinopathy, nephropathy and diabetes mellitus type II.

20 Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein  
25 (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health,  
30 National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA,  
35 1993, 269, pp. 3015-23. People who are identified as having one or more of the

above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for  
5 having an atherosclerotic disease event.

The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly the ammonium salt or crystalline calcium salt of dihydroxy open acid simvastatin, including Compounds I to V and mixtures thereof, is from about 1 to 200 mg/day, and  
10 more preferably from about 5 to about 40 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is preferred. As examples, the daily dosage amount may be selected from,  
15 but not limited to 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 100 mg, 150 mg, 160 mg and 200 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

20 For crystalline calcium salt of dihydroxy open acid simvastatin, for example Compounds I to V and mixtures thereof, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such as described above) pharmaceutical  
25 dosage forms. An oral delayed-release dosage formulation of the instant drug is preferred, and particularly an enteric overcoat surrounding a rapid-release dosage unit, or the GEM controlled-release drug delivery device with an enteric overcoat surrounding the dosage unit, and most particularly an enteric overcoat surrounding a rapid-release dosage unit. Additional suitable pharmaceutical compositions for use  
30 with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers  
35 (collectively referred to herein as "carrier" materials) suitably selected with respect to

the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, calcium metabisulphite, hydroquinone, and 7-hydroxycoumarin, particularly BHA, propyl gallate and combinations thereof, can also be added to stabilize the dosage forms; the use of at least one stabilizing agent is preferred with the instant composition. Preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly Compounds I to V and mixtures thereof. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone,

polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for preparing a pharmaceutical composition comprising combining a dihydroxy open acid statin with  
5 a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier.

In a broad embodiment, any suitable additional active agent or agents may be used in combination with the dihydroxy open acid statin in a single dosage  
10 formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a dihydroxy open acid statin. The additional active agent or agents can be lipid lowering compounds or agents having other pharmaceutical activities, or agents that have both lipid-lowering effects  
15 and other pharmaceutical activities. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and  
20 -2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; cholesterol absorption inhibitors such as SCH-58235 also known as ezetimibe and 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, which is described in U.S. Patent No.'s 5,767,115 and 5,846,966; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers;  
25 platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) agonists including the compounds commonly referred to as glitazones for example troglitazone, pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those  
30 PPAR $\gamma$  agonists outside the thiazolidinedione structural class; PPAR $\alpha$  agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual  $\alpha/\gamma$  agonists; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B<sub>12</sub> (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such  
35 as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as

vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril; calcium channel blockers such as nifedipine and diltiazam; endothelial antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands including both  
5 inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib. Additionally, the dihydroxy open acid statins of this invention, for example Compound I, may be used in combination with anti-retroviral therapy in AIDS infected patients to treat lipid abnormalities associated with such treatment, for example but not limited to their use  
10 in combination with HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir.

A therapeutically or prophylactically effective amount, as appropriate, of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example Compound I, can be used for the preparation of a medicament useful for  
15 inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as treating lipid disorders, preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or  
20 subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of crystalline calcium salt of dihydroxy open acid simvastatin, or more particularly about 5 mg to 160 mg.

A therapeutically or prophylactically effective amount, as appropriate, of a dihydroxy open acid statin can be used for the preparation of an oral medicament  
25 adapted for delayed-release, wherein substantial release of the statin after oral administration does not occur until after passage of the medicament through the stomach, or alternately wherein at least 90% of the statin is delivered in its dihydroxy open acid form to the intestinal mucosa of a patient after oral administration. Said oral medicaments are also useful for inhibiting HMG-CoA reductase, as well as for  
30 treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

The medicament comprised of a dihydroxy open acid statin, for example Compounds I to V and mixtures thereof, may also be prepared with one or more additional active agents, such as those described *supra*.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for  
5 obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by reference, describe methods for making dihydroxy open-acid and lactonized forms of simvastatin.

Compound I of the instant invention can generally be prepared as  
10 follows. Simvastatin and its dihydroxy open acid counterpart, including Compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make Compound I are performed under an inert atmosphere such as nitrogen. Although Compound I can be obtained without using an inert atmosphere, the purity of the desired product will not be  
15 optimized.

Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably neutralized before proceeding to the salt formation step in  
20 order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. Sodium hydroxide is preferred. The hydrolysis can be performed in water, an  
25 aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, n-propyl alcohol (propanol). Examples of suitable aprotic organic solvents include but are not limited to acetonitrile, dimethyl sulfoxide (DMF), N,N-dimethylformamide (DMSO), tetrahydrofuran (THF),  
30 *tert*-butyl methyl ether (MTBE) and toluene. Particularly, an aqueous ethanol or n-propyl alcohol solvent mixture may be used, and more particularly an aqueous n-propyl alcohol solvent mixture.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to about 6 to 11, particularly 6 to 9, and more particularly 7 to 8.5,  
35 by addition of an acid. In this pH range, the dihydroxy open acid simvastatin will

exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a salt that is soluble in the solvent system employed in the instant process. Preferably an acid such as acetic acid (HOAc) or a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate  $[\text{Ca}(\text{OAc})_2 \cdot x\text{H}_2\text{O}]$  in water or an aqueous-organic solvent mixture, such as aqueous EtOH, MeOH, i-PrOH, n-PrOH, acetonitrile, DMF, DMSO, THF, and particularly aqueous EtOH or aqueous n-propyl alcohol. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time with periods of aging. For example, a small portion, e.g., about one-quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C. Optionally, the reaction mixture can be seeded with crystalline Compound I.

Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in the art, for example, by examining a sample of the product under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C,

and more particularly from about 30 to 40°C, and most particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to crystallized product; however, it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

5                   If necessary, the slurry is then allowed to cool to room temperature and is collected by filtration, for example suction filtration. The recovered solid is dried under a moist atmosphere (about 30 to 70% relative humidity, particularly 40 to 70%), preferably a moist inert atmosphere such as nitrogen, and particularly at a temperature from about 10 to 40°C, and more particularly 25 to 35°C. The final step of filtration  
10 in the recovery of Compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to Compound I is performed, as described below, then the final filtration is the one performed after combining the antioxidant with Compound I.

15                   As noted above, Compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, one or more anti-oxidants such as BHA, BHT, propyl gallate, ascorbic acid, calcium metabisulphite, hydroquinone, nordihydroguaiaracetic acid (NDGA) or 7-hydroxycoumarin can be combined with  
20 Compound I. Any suitable method for combining the anti-oxidants with Compound I can be employed; for example, it can be done by agitating a slurry of Compound I with one or more of the antioxidants and recovering the resulting solid by filtration, or by washing a filtered cake of Compound I with an anti-oxidant solution.

25                   Alternatively, the ammonium salt of dihydroxy open acid simvastatin can be used as the starting material to be combined with the calcium-acetate hydrate, thus avoiding the hydrolysis and pH adjustment steps needed when starting with lactonized simvastatin. The other reaction conditions described above, such as solvents, temperatures, etc., can otherwise be employed.

30                   Based on the available data, it is believed that Compounds I, II, III and IV are crystalline hydrated forms of structure Ia, each having a different level of hydration, while Compound V is an anhydrous crystalline form of structure Ia obtained by dehydrating any of the hydrated crystalline forms of structure Ia, i.e., Compounds I to IV. Since Compounds I to V are all crystalline forms of structure Ia having varying degrees of hydration, the methods for making the different forms are

generally based on experimental conditions which have been discovered to alter the level of hydration of the Compounds while maintaining crystallinity.

For example, Compound II can be made by vacuum or suction drying Compound I or Compound III solids or mixtures thereof at 10 to 45 °C at 10 to 20 %  
5 relative humidity, preferably from 30 to 35°C at 12 to 14% relative humidity, for about 6 to 24 hours.

Compound III can be made as a wet cake containing from 50 to 70 weight% water, by filtering a crystallized slurry of calcium salt of dihydroxy open acid simvastatin. For example, a slurry of calcium salt of dihydroxy open acid  
10 simvastatin in water or in an aqueous organic solvent mixture can be generated employing the general procedures described in Examples 1, 3 or 7 for making a calcium salt slurry. The Compound III wet cake containing from 50 to 70 weight% water can be partially dried down to a solid containing 10 to 70 weight% of water at a temperature from 10 to 40°C, at 30 to 90% relative humidity, preferably from 25 to  
15 30°C at 30 to 70% relative humidity, for about 1 to 24 hours and still be maintained as Compound III. Alternatively, Compounds I, II, IV, or V or mixtures thereof can be converted into Compound III slurry by re-slurrying Compound I, II, IV or V or mixtures thereof in water or an aqueous organic solvent mixture, for several hours at a temperature from 0 to 50 °C, preferably from 25 to 35 °C. Amorphous calcium salt of  
20 dihydroxy open-acid simvastatin can be converted into Compound III slurry by re-slurrying the amorphous salt form in water or aqueous organic solvent mixtures for several hours at a temperature from 20 to 50 °C, preferably from 30 to 40°C, for about 10 hours. Examples of aqueous organic solvent mixtures that can be used in the above procedures for making Compound III include but are not limited to aqueous n-  
25 PrOH or aqueous EtOH, and particularly aqueous n-PrOH such as 10% n-PrOH..

Compound IV can be made by vacuum or suction drying Compound I, Compound II or Compound III solids or mixtures thereof at a temperature from 45 to 65 °C at 10 to 0 % relative humidity, preferably from 50 to 60 °C at 0 to 5 % relative humidity, for about 6 to 24 hours.

30 Compound V is made by dehydrating hydrated crystalline calcium salt of dihydroxy open acid simvastatin. For example, Compound V can be made by vacuum or suction drying Compound I, Compound II, Compound III or Compound IV solids or mixtures thereof at a temperature from 65 to 90 °C at 5 to 0 % relative humidity, preferably from 70 to 75 °C at 0% relative humidity, for about 6 to 24  
35 hours.

Abbreviations which may appear herein are as follows: MeOH is methanol; EtOH is ethanol; PrOH is propanol; HOAc is acetic acid; MeCN is acetonitrile; DMF is dimethyl sulfoxide; DMSO is N,N-dimethylformamide; Ca(OAc)<sub>2</sub> is calcium acetate; HPLC is high performance liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity, %A is area percent. The "seed" used in the examples for making Compound I is Compound I. The symbol " $\pm$ " means plus or minus.

10

### EXAMPLE 1

#### Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

15 A 22 L four-necked round bottom flask was equipped with a temperature probe, a N<sub>2</sub> inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H<sub>2</sub>O was added and the solution was purged with N<sub>2</sub> for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N<sub>2</sub> for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, 20 the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)<sub>2</sub>·H<sub>2</sub>O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H<sub>2</sub>O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at 25 room temperature for 30 min, and then at 30 to 35°C for 1-2 h.

The rest of Ca(OAc)<sub>2</sub> in EtOH-water was added over approx. 30 min at 30 to 35°C. The slurry was aged at 30 to 35 °C for 5 hours under atmosphere of N<sub>2</sub>. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H<sub>2</sub>O, 4 L 20% EtOH-H<sub>2</sub>O, followed 30 by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N<sub>2</sub> (40 to 70% relative humidity) at room temperature for 4 days. Crystalline hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned delumper.

### HPLC CONDITIONS

5

Column: YMC Basic 4.6 mm x 25 cm

Detector: ABS 757 1AU/volt output

Sample solvent: EtOH/CH<sub>3</sub>CN/H<sub>2</sub>O (1:1:1)

Column temp: 25 °C (The column may also be at 5 °C to prevent formation of simvastatin on column).

10

Flow rate: 1 .5 mL / min.

Wavelength: 238 and 210 nm

Gradient:

15

Time (min.)    %CH<sub>3</sub>CN

%H<sub>2</sub>O (10 mM 2HPO<sub>4</sub>-  
KH<sub>2</sub>PO<sub>4</sub>, pH = 6.5)

0.00            30            70

20.00           45            55

34.00           70            30

39.00           70            30

20

39.50           30            70

43.00           30            70

Retention time of simvastatin open acid: 17.07 min.

Retention time of simvastatin: 32.90 min.

25

### SPECTRAL DATA

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.61 - 1.55 (m, 2 H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19 (m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

30

<sup>13</sup>C NMR (100.55 MHz, CD<sub>3</sub>OD),  $\delta$  182.3, 179.3, 134.1, 133.2, 130.3, 129.6, 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

5 EI MS: m/e: 437 (M+H), 419(M+H-H<sub>2</sub>O), 303.

HR-EI MS: Calculated for C<sub>25</sub>H<sub>38</sub>O<sub>5</sub> 418.2719; Found: 418.2712.

## EXAMPLE 2

10 Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) with BHA

A 22 L three-necked round bottom flask was equipped with a temperature probe, a N<sub>2</sub> inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H<sub>2</sub>O was added and purged with N<sub>2</sub> for 10 min. Simvastatin (396 g, 0.946  
15 mol) was added, and the slurry purged with N<sub>2</sub> for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction is usually complete in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L  
20 of 60% EtOH- H<sub>2</sub>O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room temperature for 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the Ca(OAc)<sub>2</sub> in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere of N<sub>2</sub>. The slurry was allowed to cool to room  
25 temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H<sub>2</sub>O, 4 L 20% EtOH-H<sub>2</sub>O, followed by 6 L x 3 of D.I. water. The solid was suction dried under atmosphere of moist N<sub>2</sub> (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

The above wet cake was placed in a clean 20 L three necked flask  
30 under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H<sub>2</sub>O (8.5 L) was added, followed by addition of degassed water (2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration under atmosphere of moist N<sub>2</sub> with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N<sub>2</sub> (40 to

70% RH) at room temperature for 4 days. The calcium salt title product was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

### EXAMPLE 3

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) in aqueous nPrOH: Conventional addition mode

Step 1: Hydrolysis

10

A 72 L three-necked round bottom flask was equipped with a temperature probe, a N<sub>2</sub> inlet, an additional funnel, and an overhead stirrer. 28.5 L of D.I. H<sub>2</sub>O was added and purged with N<sub>2</sub> for 10 min. 1.5 Kg simvastatin was added, followed by 788mL of 5N NaOH in one portion at room temperature. The hydrolysis reaction is usually complete in 2 h. as analyzed by HPLC (> 99.9% conversion). 1.5L of nPrOH was added and the pH of the reaction solution was adjusted to 9.5 to 11.0 by adding 2 N HOAc (about 170 mL).

15

Step 2: Salt Formation

150 g of seed (Compound I) was added to the above solution and the resulting slurry was allowed to warm up to 35 to 40 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (347 g) in 15 L of 20% nPrOH was purged with nitrogen for 5min. and added to slurry over 3 h. The resulting slurry was aged at 35 to 40 °C for 5 h. under an atmosphere of N<sub>2</sub> and then cooled to room temperature. The solid was collected by filtration and was washed with 10% nPrOH-H<sub>2</sub>O (15 L x 3).

20

Step 3: BHA loading

The above wet cake (9.1 kg) was transferred into a clean 72 L three necked flask under an atmosphere of nitrogen. A solution of BHA (7.6 g) in degassed 10% nPrOH (45 L) was added and the slurry was agitated at room temperature for 1 h. and filtered under atmosphere of N<sub>2</sub>, and then suction dried under atmosphere of moist N<sub>2</sub> (30 to 70% RH) at room temperature for 7 days. 1.78 Kg of Ca salt title product was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 6.6 %wt).

25

30

### EXAMPLE 4

Preparation of hydrated crystalline calcium salt of dihydroxy open acid simvastatin in aqueous PrOH: Simultaneous addition mode

5 The process described in this example allows for keeping a portion of the batch in the vessel at all times as seed in a semi-continuous process.

100 g of simvastatin was hydrolyzed in 1.9 L water as described in Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to 11 with 1 N HOAc. The resulting solution and a solution of  $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (23.2 g) in 1.0 L of 20% nPrOH were added separately but simultaneously to a suspension of 10-50 wt% Ca salt in 10% nPrOH (30 volume 10% PrOH relative to the amount of the seed) at 30 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled to room temperature, filtered, and loaded with anti-oxidant and dried as described in conventional addition mode process. 95% yield.

15

#### EXAMPLE 5

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous PrOH: Loading BHA through co-crystallization

Method A: 100 g of simvastatin was hydrolyzed in 1.9 L water as described in Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 35 to 40 °C. A solution of  $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (23.2 g) and BHA (540 mg) in 1.0 L of 20% nPrOH were added to the slurry at 35 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled to room temperature, filtered and washed with a solution of BHA (0.1g/L) in 10% nPrOH (1L x 3). The wet cake was dried under moist  $\text{N}_2$  as described in conventional addition mode process. The final dried Ca salt title product contained 0.2wt% BHA. 95% yield.

Method B: The procedure of Method A was employed with the following change. Instead of adding BHA to a  $\text{Ca}(\text{OAc})_2$  solution, the same amount of BHA was added into the pH adjusted solution of hydrolyzed simvastatin at room temperature. The solution was warmed to 35 to 40 °C to dissolve BHA. Then, 10wt% seed was introduced. The rest of the steps were as described in Method A. The final dried Ca salt title product contained 0.2wt% BHA. 95% yield.

35

#### EXAMPLE 6

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) in aqueous PrOH: Loading BHA/propyl gallate

Starting with 2.0 Kg of simvastatin, the calcium salt of dihydroxy open  
5 acid simvastatin was crystallized, isolated, and washed as described in Example 3.  
The first wet cake was transferred to a clean 100L vessel under atmosphere of N<sub>2</sub>. A  
solution of BHA (9.2g) and propyl gallate (11.2 g) in 50 L 10% nPrOH was added to  
above vessel. The slurry was aged at room temperature for 1h. The slurry was filtered  
with no wash. The wet cake was dried under moist N<sub>2</sub>. 95% yield. The dried salt was  
10 loaded with 0.07wt% propyl gallate and 0.2 wt% BHA.

EXAMPLE 7

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
15 (Compound I) in aqueous PrOH: Loading propyl gallate

Starting with 2.0 Kg of simvastatin, the calcium salt of dihydroxy open  
acid simvastatin was crystallized, isolated, and washed as described in Example 3.  
Then, the wet cake was washed with 10L of a solution of propyl gallate in 10%  
nPrOH (propyl gallate concentration = 0.224 g/L). Then, 20 L of propyl gallate  
20 solution in 10% nPrOH (propyl gallate concentration = 0.224 g/L) was added and the  
wet cake was mixed in the filtration pot before filtration. The wet cake was dried  
under moist N<sub>2</sub>. 95% yield. The dried salt was loaded with 0.07wt% propyl gallate.

EXAMPLE 8

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Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) Loading BHA, BHA/Vitamin E, and Vitamin E in heptane

100 g of simvastatin was hydrolyzed in 1.9 L water as described in  
30 Example 3. Then, 100 ml nPrOH was added and the solution pH was adjusted to 9 to  
11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to  
35 to 40 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (23.2 g) in 1.0 L of 20% nPrOH was added  
to a slurry at 35 to 40 °C over 3 h. After 5 h age at 30 to 40 °C, the slurry was cooled  
to room temperature. The calcium salt slurry was filtered and washed with 10%  
35 nPrOH (500 mL x 1), followed by water (1L x 3). The wet cake (KF = 75 to 80 wt%

water) was then washed with 1 L of heptane, to displace most of the water. This wet cake was washed with a solution of BHA or Vitamin E or BHA/Vitamin E (conc. = 1.38 g/L, 800 mL) and dried under moist N<sub>2</sub>.

5

## EXAMPLE 9

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous MeCN

10 A 7.2 L three-necked round bottom flask was equipped with a temperature probe, a N<sub>2</sub> inlet, an additional funnel, and an overhead stirrer. 2.1 L of D.I. H<sub>2</sub>O was added and purged with N<sub>2</sub> for 10 min. 150 g simvastatin was added, followed by 78.8 mL of 5N NaOH in one portion at room temperature. The hydrolysis reaction is usually complete in 2 h. as analyzed by HPLC (> 99.9% conversion). 900 mL of MeCN was added and the pH of the reaction solution was adjusted to 9.5 to 15 11.0 by adding 2 N HOAc (about 17 mL).

30.0 g crystalline seed was added to above solution and the resulting slurry was allowed to warm up to 30 to 35 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (34.7 g) in 1.5 L of 30% MeCN was purged with nitrogen for 5 min. and added to reaction slurry over 3 h. The slurry was at 35 to 40 °C for 5 h. under atmosphere of N<sub>2</sub>. The 20 slurry was allowed to cool to room temperature and the solid was collected by filtration. The wet cake was washed with 30% MeCN (1.5 L) and 10% MeCN (1.0 L), and rinsed/washed with a solution of BHA (0.9 g/L) in degassed 10% MeCN (1.0 L x 2). The solid was suction dried under atmosphere of moist N<sub>2</sub> (30 to 70% RH) at room temperature for 5 days. 1.67 Kg of the title compound was obtained as a white 25 powder (88% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 6.6 %wt).

## EXAMPLE 10

30 Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) in aqueous MeOH

50 g simvastatin was hydrolyzed in 850 mL water as described in Example 3. Then, 150 ml MeOH was added and the solution pH was adjusted to 7 to 11 with 1N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 30-35 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (11.6 g) in 500 mL of 30% MeOH was added 35 to the slurry at 30-35 °C over 3 h. After 5 h age at 30-35 °C, the slurry was cooled to

room temperature. The dihydroxy open acid simvastatin calcium salt slurry was filtered and washed with 20% MeOH (200 ml) and water (500 ml x 3). The wet cake was dried under moist N<sub>2</sub>. The final dried Ca salt title product was isolated in 96% yield.

5

### EXAMPLE 11

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) in aqueous i-PrOH, DMF, DMSO

10 50 g simvastatin was hydrolyzed in 850 mL water as described in Example 3. Then, 150 ml i-PrOH was added and the solution pH was adjusted to 7 to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 30-35 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (11.6 g) in 500 mL of 30% i-PrOH was added to the slurry at 30-35 °C over 3 h. After 5 h age at 30-35 °C, the slurry was cooled to  
15 room temperature. Ca salt slurry was filtered and washed with 20% ml i-PrOH (200 ml) and with water (500 ml x 3). The wet cake was dried under moist N<sub>2</sub>. The final dried Ca salt title product was isolated in 96% yield.

The same procedure could be applied to prepare Compound I in DMF, DMSO, and similar solvents.

20

### EXAMPLE 12

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) in water

25 50 g of simvastatin was hydrolyzed in 1.0 L water as described in Example 3. Then, the solution pH was adjusted to 11 with 1 N HOAc. 10wt% seed was added and the slurry was allowed to warm up to 35-40 °C. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (11.6 g) in 500 mL of water was added to the slurry at 35-40 °C over 5 h. After 10 h age at 35-40 °C, the slurry was cooled to room temperature. Ca salt  
30 slurry was filtered and washed with water (500 ml x 3). The wet cake was dried under moist N<sub>2</sub>. The final dried Ca salt title product was isolated in 96% yield.

### EXAMPLE 13

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin  
(Compound I) from dihydroxy open acid simvastatin ammonium salt

Method A: 50 g of dihydroxy open acid simvastatin ammonium salt was dissolved into 800 ml of 25% nPrOH which was then added dropwise to a solution of  $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10.7 g) in 75 ml of water at room temperature over 2h. The resulting slurry was aged at 30 to 35 °C 5 h. After cooling to room temperature, the slurry was isolated by filtration. The wet cake was washed with 10% nPrOH (500 ml x 3). The wet cake was loaded with antioxidants and dried under moist  $\text{N}_2$  as described above to give the title product.

Method B: 50 g of dihydroxy open acid simvastatin ammonium salt was added into a solution of  $\text{Ca}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10.7 g) in 1.5 L of 10% nPrOH in one portion at room temperature. The resulting slurry was aged at 30 to 35 °C 5 h. After cooling to room temperature, the slurry was isolated by filtration. The wet cake was washed with 10% nPrOH (500 ml x 3). The wet cake was loaded with antioxidants and dried under moist  $\text{N}_2$  as described above to give the title product.

By using both Methods A and B described as above, the title product could also prepared from ammonium salt in the following aqueous solvents: acetone, MeOH, EtOH, iPrOH, , MeCN, neat water, DMF, DMSO, and similar solvents.

#### EXAMPLE 14

##### Recrystallization Procedure Using nPrOH-H<sub>2</sub>O

Dried Compound I (21 g) was dissolved in 150ml of 40% nPrOH at 35°C and line filtered. This solution was added dropwise to a slurry of 10 wt% seed in 480 ml of 4% PrOH at 35 to 40°C over 3 to 5 h. After aging overnight at 35 to 40°C, the slurry was allowed to cool to room temperature. The solid was filtered and washed with 10% nPrOH (200ml x 2). The wet cake was dried under moist  $\text{N}_2$ . 95% yield.

#### EXAMPLE 15

##### Recrystallization Process Using EtOH-H<sub>2</sub>O

Method A: 25 g of Compound I was dissolved into 425ml of 95% EtOH at 40 °C and line filtered. The filtered solution was added dropwise to 825ml of water in the presence of 10% wt seed at 30 to 35 °C over 3 to 5 h. The slurry was aged

overnight and cooled to 0 to 5 °C before filtration. The wet cake was washed with 250 ml of 30% EtOH and dried under moist N<sub>2</sub> at room temperature. 92% yield.

Method B: 25 g of Compound I was dissolved into 625ml of 95% EtOH at 30 to 40 °C and line filtered. 525 ml of water was added at 30 to 40 °C. After adding 10wt% seed, 825 ml of water was added dropwise at 30 to 40 °C over 3 h. The slurry was aged overnight and cooled to 0 to 5 °C before filtration. The wet cake was washed with 250 ml of 30% EtOH and dried under moist N<sub>2</sub> at room temperature. 92% yield.

10

### EXAMPLE 16

#### Preparation of Compound II

30 Grams of Compound I solids (made by the procedure in Example 1) were placed inside a jacketed vessel. The vessel jacket was set at 35°C and the system pressure was adjusted to 5-6 mmHG composed entirely of water vapor. The solids were exposed to these conditions for approximately 90 hours. The final product was verified to be Compound II by DSC.

Compound II was also obtained following the same procedure described above, but substituting Compound III in place of Compound I as the starting material.

### EXAMPLE 17

#### Preparation of Compound III

Method A: Compound III was obtained by filtering a slurry of crystalline calcium salt of dihydroxy open-acid simvastatin in aqueous n-PrOH, and recovering the wet cake containing 50-70 wt% water. The wet cake was confirmed to be Compound III by solid state <sup>13</sup>C NMR.

Method B: Compound I (10 g) was re-slurried in 200 ml water at room temperature for 1 hour. Filtration provided Compound III as a wet cake (50 to 70 wt% water).

Method C: 10 g of amorphous calcium salt of dihydroxy open-acid simvastatin was slurried in 300 ml of 10% n-PrOH at 35 to 40°C for 10 hours. The slurry was allowed to cool to room temperature. Filtration provided Compound III as a wet cake (50 to 70 wt% water).

5

### EXAMPLE 18

#### Preparation of amorphous calcium salt of dihydroxy open acid simvastatin

A 1 L three-necked round bottom flask was equipped with a temperature probe, a N<sub>2</sub> inlet, an additional funnel, and an overhead stirrer. 475 mL of D.I. H<sub>2</sub>O was added and purged with N<sub>2</sub> for 10 min. 25 g Simvastatin was added, followed by 13.3 mL of 5N NaOH in one portion at room temperature. The hydrolysis reaction is usually complete in 2 h. as analyzed by HPLC (> 99.9% conversion). 25 mL of n-PrOH was added and the pH of the reaction solution was adjusted to 9.0 to 11.0 by adding 1 N HOAc. A solution of Ca(OAc)<sub>2</sub>•H<sub>2</sub>O (5.8 g) in 250 mL of D.I. H<sub>2</sub>O was purged with nitrogen for 5 minutes and added to the above pH adjusted solution at 0 -10 °C over 30 min. The resulting slurry was aged at 0 -10°C for 15 min. The solid was collected by filtration and was washed with H<sub>2</sub>O (100ml). The wet cake was suction dried under N<sub>2</sub> at room temperature for 12 h to provide 26 g of the title compound.

### EXAMPLE 19

#### Preparation of Compound IV

Compound I was dried in a vacuum oven under dry N<sub>2</sub> from 50 to 60°C at 30 mmHg for 1 day to provide Compound IV. The product was confirmed to be Compound IV by DSC and XRPD pattern.

Compound IV was also obtained following the same procedure described above, but substituting Compound II or III in place of Compound I as the starting material.

### EXAMPLE 20

#### Preparation of Compound V

Compound I was vacuum oven dried (30 mmHg) under dry N<sub>2</sub> from 70 to 75°C for one day to provide Compound V. The product was confirmed to be Compound V by DSC and XRPD pattern.

- 5      Compound V was also obtained following the same procedure described above, but substituting Compound II, III or IV in place of Compound I as the starting material.

## EXAMPLE 21

- 10    An open, randomized, four-period, crossover study to compare the effect of itraconazole on the single-dose pharmacokinetics of intraduodenally administered dihydroxy open acid simvastatin versus orally administered simvastatin in healthy male subjects
- 

- 15    Objectives:    (1) To determine the effect of itraconazole, a potent CYP3A inhibitor, on the plasma AUC of active and of total HMG-CoA reductase inhibitory activity following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin; (2) to determine and compare the dose-adjusted plasma AUC of  
20    active HMG-CoA reductase inhibitory activity following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin versus a single oral administration of simvastatin 20-mg film coated tablet (FCT); (3) to determine the effect of itraconazole on the plasma AUC's of dihydroxy open acid simvastatin and of simvastatin lactone concentration following a single intraduodenal dose of a solution containing 5 mg dihydroxy open acid simvastatin.

- 25    Study Design: This study was designed in an open, four-period crossover randomized fashion. Twelve healthy male subjects received four treatments (A, B, C and D). In Treatment A, subjects received itraconazole 200 mg (2 x 100-mg capsule) for 4 days followed by a single dose of 5-mg dihydroxy open acid simvastatin solution  
30    administered intraduodenally on day 4, 1 hour after the fourth daily dose of itraconazole. In Treatment B, subjects were given a single dose of 5-mg dihydroxy open acid simvastatin solution administered intraduodenally on day 1. Intraduodenal administration was accomplished via a nasoduodenal tube placed under fluoroscopic guidance by an experienced gastroenterologist just prior to dosing and removed  
35    following the 1-hr post dose measurements. Treatments C and D were similar to those

of Treatments A and B, except that orally dosed simvastatin 20-mg conventional film coated tablet was used. The wash out between treatment periods was at least 7-days following a treatment containing itraconazole or at least 3 days following a treatment without itraconazole. Plasma samples were collected at appropriate time intervals for up to 24 hours following simvastatin or dihydroxy open acid simvastatin administration, for analysis of total and active HMG-CoA reductase inhibitory activities as well as for simvastatin and dihydroxy open acid simvastatin concentrations.

10 Analytical Methodology: Plasma concentrations of simvastatin and dihydroxy open acid simvastatin acid were determined simultaneously by an improved liquid chromatography/tandem mass spectrometry (LC/MS/MS) method using lovastatin and dihydroxy open acid lovastatin acid as internal standards. An enzymatic assay method was used to determine plasma concentrations of active and total (active plus potentially active) HMG-CoA reductase inhibitory activity.

Pharmacokinetics: The area under the plasma concentration-time profile from time zero to the last sampling time (AUC<sub>0-last</sub>) was calculated using linear trapezoidal rule. The apparent elimination rate constant (k) of simvastatin and dihydroxy open acid simvastatin was estimated by least-squares regression analysis of the log-linear portion of the simvastatin and dihydroxy open acid simvastatin concentration-time data, and the apparent elimination half-life ( $t_{1/2}$ ) was calculated as  $t_{1/2} = 0.693/k$ . All calculations were based on designated sampling times or actual sampling times when they differed from the designated times by more than 10 minutes.

Discussion of Results: This was an open, randomized, four-period crossover study in twelve healthy male subjects. The results showed that intraduodenal administration of dihydroxy open acid simvastatin 5-mg solution yielded higher (~4-fold) dose-adjusted plasma AUC of the active HMG-CoA reductase inhibitory activity than oral administration of simvastatin 20-mg tablet (Table 9). Following dihydroxy open acid simvastatin administration, the unchanged dihydroxy open acid simvastatin was the major component (~60%), while simvastatin was a minor component (<10%) contributing to plasma HMG-CoA reductase inhibitory activity. As evident by comparable AUC values for both the total and active inhibitors (see Table 9) as well as low plasma levels of simvastatin in plasma (AUC <10% of dihydroxy open acid

simvastatin AUC) (see Table 11), lactonization of either dihydroxy open acid simvastatin or its active metabolites occurred minimally following intraduodenal administration of dihydroxy open acid simvastatin. Pretreatment with itraconazole caused minimal changes (1.3-1.5-fold) in the systemic exposure as measured by AUC and C<sub>max</sub> of HMG-CoA reductase inhibitory activity (total or active) following administration of dihydroxy open acid simvastatin 5-mg intraduodenally, as compared to that observed following oral administration of simvastatin 20-mg tablet (1.3-3.8-fold) (see Table 10). When measured as the unchanged drug, the effect of itraconazole observed following dihydroxy open acid simvastatin administration was also minimal (1.5-fold) and was much less than the corresponding measure obtained following simvastatin administration (19-fold) (see Table 11). A moderate effect (3-4-fold increase) was noted for the AUC and C<sub>max</sub> of simvastatin following treatment with itraconazole prior to dihydroxy open acid simvastatin administration (see Table 11). However, apparent t<sub>1/2</sub> values for dihydroxy open acid simvastatin or simvastatin were essentially unchanged by itraconazole (see Table 11). Overall, these results indicate that the pharmacokinetics of dihydroxy open acid simvastatin is less prone to alteration by itraconazole, a potent CYP3A inhibitor, than that of simvastatin in humans. From these results it appears that dihydroxy open acid simvastatin, although a substrate for CYP3A, is metabolized with a much lower intrinsic clearance than that of simvastatin in human liver microsomes.

TABLE 9

- Pharmacokinetic parameters for total and active HMG-CoA reductase inhibitors following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally (ID) or 20-mg simvastatin (SV) tablet orally (FCT) to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

	Drug Administered	5 mg SVA (ID)	20 mg SV (FCT)
	N	12	12
AUC (ng eq. hr/ml)	Total	56.0 (28.6)	180.7 (57.2)
	Active	54.1 (28.5)	59.7 (18.1)
	SV	1.02 (0.5)	16.9 (10.5)
	SVA	33.9 (16.7)	7.7 (4.9)
Cmax (ng eq./ml)	Total	6.2 (3.6)	67.1 (27.2)
	Active	5.7 (3.0)	16.1 (4.4)
	SV	0.13 (0.05)	6.84 (4.6)
	SVA	3.78 (1.93)	0.92 (0.58)
Tmax (hr)	Total	3.3 (2.3)	1.2 (0.5)
	Active	3.6 (2.5)	1.4 (0.5)
	SV	4.9 (2.0)	1.1 (0.5)
	SVA	4.1 (2.1)	3.7 (2.1)
t1/2 (hr)	SV	6.7 (1.7) n=8	4.2 (1.9)
	SVA	2.3 (0.5)	3.5 (1.0)

TABLE 10

Pharmacokinetic parameters for total HMG-CoA reductase inhibitor following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally (ID) or 20-mg simvastatin (SV) tablet orally (CT) with or without pretreatment with itraconazole (2x100-mg capsule, qd) for 4 days to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

Treatment	AUC (ng eq.hr/mL)	Cmax (ng eq/mL)	Tmax (hr)
<b>Total Inhibitors</b>			
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	86.1 ± 47	8.2 ± 4.0	4.3 ± 2.2
Single 5-mg SVA (ID)	56.0 ± 28.6	6.2 ± 3.6	3.3 ± 2.3
Geometric Mean Ratio	1.5	1.3	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	683 ± 232	126 ± 54.8	1.9 ± 0.9
Single 20-mg SV (CT)	180.7 ± 57.2	67.1 ± 27.2	1.2 ± 0.5
Geometric Mean Ratio	3.8	1.9	
<b>Active Inhibitors</b>			
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	75.0 ± 39.6	7.4 ± 3.9	5.5 ± 1.7
Single 5-mg SVA (ID)	54.1 ± 28.5	5.7 ± 3.0	3.6 ± 2.5
Geometric Mean Ratio	1.3	1.3	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	195 ± 104	23.0 ± 13.6	3.1 ± 0.9
Single 20-mg SV (CT)	59.7 ± 18.1	16.1 ± 4.4	1.4 ± 0.5
Geometric Mean Ratio	3.1	1.3	

TABLE 11

Pharmacokinetic parameters for simvastatin or dihydroxy open acid simvastatin following administration of 5-mg dihydroxy open acid simvastatin (SVA) intraduodenally (ID) or 20-mg simvastatin (SV) tablet orally (CT) with or without pretreatment with itraconazole (2x100-mg capsule, qd) for 4 days to 12 healthy male volunteers. Results are means from 12 subjects. Values in parentheses are SD.

Treatment	AUC (ng eq.hr/mL)	Cmax (ng eq/mL)	t1/2 (hr)	Tmax (hr)
<b>Simvastatin</b>				
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	5.18 ± 3.15	0.43 ± 0.2	6.7 ± 2.5 (n=11)	5.3 ± 1.9
Single 5-mg SVA (ID)	1.02 ± 0.5	0.13 ± 0.05	6.7 ± 1.7 (n=8)	4.9 ± 2.0
Geometric Mean Ratio	4.4	3.2	1.0	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	316 ± 142	77.2 ± 50.7	5.2 ± 1.5	1.8 ± 1.1
Single 20-mg SV (CT)	16.9 ± 10.5	6.84 ± 4.6	4.2 ± 1.9	1.1 ± 0.5
Geometric Mean Ratio	19.4	11.4	1.3	
<b>Simvastatin Acid</b>				
Single 5-mg SVA (ID) + 4 Days of Daily 200-mg Itraconazole	56.8 ± 33.5	5.78 ± 3.27	2.8 ± 1.1	4.7 ± 2.4
Single 5-mg SVA (ID)	33.9 ± 16.7	3.78 ± 1.93	2.3 ± 0.5	4.1 ± 2.1
Geometric Mean Ratio	1.5	1.5	1.1	
Single 20-mg SV (CT) + 4 Days of Daily 200-mg Itraconazole	86.2 ± 65.6	9.76 ± 7.38	4.5 ± 1.3	4.0 ± 1.4
Single 20-mg SV (CT)	7.70 ± 4.9	0.92 ± 0.58	3.5 ± 1.0	3.7 ± 2.1
Geometric Mean Ratio	11.0	10.7	1.3	

10

## EXAMPLE 22

Spectral Fitting

Analysis of <sup>13</sup>C solid-state NMR spectra of Compounds I, II, III, IV and V active pharmaceutical ingredient (API) and formulated product yields the composition by fitting the unknown spectrum to a linear combination of reference spectra. The reference spectra represent a specific mass (100 mg) of each component measured under identical conditions on the NMR. It has been shown that the spectral intensity scales linearly with the mass of material measured and that prepared

mixtures of Compounds I to V API have NMR spectra which are simply a weighted sum of the individual reference spectra. The composition of unknown mixtures can be determined by linear least-squares fitting using a fitting equation which takes the form

5

$$\text{Unknown(ppm)} = W_a * \text{Reference}_a(\text{ppm}) + W_b * \text{Reference}_b(\text{ppm}) + W_c * \text{Reference}_c(\text{ppm}) \dots \quad (1)$$

where W is the weight of each Reference spectrum for each component (a,b, and c).  
10 Each data point (ppm) in the unknown spectrum is a weighted sum of the reference spectra at that point. Analysis of the spectrum consists of fitting greater than 140 simultaneous linear equations to determine 6 unknowns (number of reference spectra + baseline correction + ppm shift). This is an overdetermined problem from which a unique solution can be obtained when the reference spectra are unique. The presence  
15 of each of the crystalline Compounds I, II and/or III in API bulk product or in a formulated drug product can be determined using only the carbonyl region from 174 to 180 ppm.

The presence of Compounds IV, V or the amorphous form of the calcium salt of dihydroxy open-acid simvastatin in API bulk product or in a  
20 formulated drug product can also be determined using only the carbonyl region from 174 to 180 ppm, although such spectra obtained using the technology employed herein cannot distinguish between Compounds IV, V and the amorphous calcium salt compound.

While the invention has been described and illustrated with reference  
25 to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any  
30 of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon whether there are present pharmaceutical carriers, as well as the type of formulation employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the  
35 present invention. It is intended, therefore, that the invention be defined by the scope

of the claims that follow and that such claims be interpreted as broadly as is reasonable.

## WHAT IS CLAIMED IS:

1. A compound which is a crystalline form of the calcium salt of dihydroxy open acid simvastatin.
2. The compound of claim 1 which is characterized by solid-state  $^{13}\text{C}$  nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 179.4, 179.0 (broad), 178.3, 177.9 (broad), 177.0, 176.7, 176.0 and 175.1.
3. The compound of claim 2 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 5.
4. The compound of claim 3 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 4.
5. The compound of claim 2 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 7.
6. The compound of claim 5 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 6.
7. The compound of claim 1 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having a chemical shift difference of 0.9 or 3.2 between the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance.
8. The compound of claim 7 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having chemical shift differences of 0.9, 1.6, 1.9, 2.8, 3.2, 3.9, and 4.3 between the lowest ppm carbonyl carbon resonance and other carbonyl carbon resonances.
9. The compound of claim 1 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of  $52 \pm 2^\circ$ ,  $77 \pm 2^\circ$  and  $100 \pm 2^\circ\text{C}$  obtained under a nitrogen flow bubbled through  $16.0^\circ\text{C}$  water at a heating rate of  $10^\circ\text{C}/\text{minute}$  in an open cup.

- 5                   10.     The compound of claim 9 characterized by a differential scanning calorimetry curve additionally having endotherms with peak temperatures of  $222 \pm 2^\circ$  and  $241 \pm 2^\circ\text{C}$ .
- 10                   11.     The compound of claim 1 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of  $52$ ,  $77$  and  $100^\circ\text{C}$  obtained under a nitrogen flow bubbled through  $16.0^\circ\text{C}$  water at a heating rate of  $10^\circ\text{C}/\text{minute}$  in an open cup.
12.     The compound of claim 11 characterized by a differential scanning calorimetry curve additionally having endotherms with peak temperatures of  $222$  and  $241^\circ\text{C}$ .
- 15                   13.     The compound of claim 1 characterized by the differential scanning calorimetry curve shown in Figure 2.
14.     The compound of claim 1 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of  $50 \pm 2^\circ\text{C}$ ,  $73 \pm 2^\circ\text{C}$ , and  $98 \pm 2^\circ\text{C}$ , obtained in an open cup heated to  $220^\circ\text{C}$  at a heating rate of  $2^\circ\text{C}/\text{min}$  under a nitrogen flow bubbled through water at  $19.0^\circ\text{C}$ .
- 20                   15.     The compound of claim 14 characterized by a differential scanning calorimetry curve additionally having an endotherm with a peak temperature of  $201 \pm 2^\circ\text{C}$ .
- 25                   16.     The compound of claim 14 characterized by a differential scanning calorimetry curve wherein the  $50 \pm 2^\circ\text{C}$  endotherm has an onset temperature of  $46 \pm 2^\circ\text{C}$ , the  $73 \pm 2^\circ\text{C}$  endotherm has an onset temperature of  $66 \pm 2^\circ\text{C}$ , and the  $98 \pm 2^\circ\text{C}$  endotherm has an onset temperature of  $89 \pm 2^\circ\text{C}$ .
- 30                   17.     The compound of claim 16 characterized by a differential scanning calorimetry curve additionally having an endotherm with an onset temperature of  $190 \pm 2^\circ\text{C}$  and a peak temperature of  $201 \pm 2^\circ\text{C}$ .
- 35

18. The compound of claim 14 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of 50°C, 73°C, and 98°C, obtained in an open cup heated to 220 °C at a heating rate of 2°C/min under a nitrogen flow bubbled through water at 19.0°C.

5

19. The compound of claim 18 characterized by a differential scanning calorimetry curve additionally having an endotherm with a peak temperature of 201°C.

10

20. The compound of claim 18 characterized by a differential scanning calorimetry curve wherein the 50°C endotherm has an onset temperature of 46°C, the 73°C endotherm has an onset temperature of 66°C, and the 98°C endotherm has an onset temperature of 89°C.

15

21. The compound of claim 20 characterized by a differential scanning calorimetry curve additionally having an endotherm with an onset temperature of 190°C and a peak temperature of 201°C.

20

22. The compound of claim 1 characterized by the differential scanning calorimetry curve shown in Figure 8.

25

23. The compound of claim 1 having a thermogravimetry curve obtained under a nitrogen flow at a heating rate of 10°C/minute characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C.

24. The compound of claim 1 characterized by the thermogravimetry curve shown in Figure 1.

30

25. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing an angle 2 theta value of 17.3 – 17.4°.

26. The compound of claim 25 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing an angle 2 theta value of 17.30 – 17.42°.

5 27. The compound of claim 26 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing an angle 2 theta value of 17.299 – 17.418°.

28. The compound of claim 25 having an x-ray powder diffraction  
10 pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 13.1 – 13.2° and 17.3 – 17.4°.

29. The compound of claim 25 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values:  
15 12.0°, 14.5 – 14.6°, 15.2° and 17.3 – 17.4°.

30. The compound of claim 25 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 13.1 – 13.2°, 17.3 – 17.4°, 18.0°, 19.3° and 19.7 – 19.8°.

20 31. The compound of claim 25 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 7.9°, 13.1 – 13.2°, 14.5 – 14.6°, 17.3 – 17.4° and 18.0°.

25 32. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 3.6°, 7.9°, 13.1 – 13.2° and 14.5 – 14.6°.

30 33. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 3.6°, 7.9°, 10.2 – 10.3°, 12.0°, 13.1 – 13.2°, 14.5 – 14.6°, 14.8 – 14.9°, 15.2°, 17.3 – 17.4°, 18.0°, 19.3° and 19.7 – 19.8°.

34. The compound of claim 1 having an x-ray powder diffraction  
35 pattern obtained using CuK $\alpha$  radiation characterized by reflections at d-spacings of

30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

35. The compound of claim 1 containing about 2.8 to 3.6 moles of water per mole of calcium.

36. The compound of claim 1 which is characterized by solid-state  $^{13}\text{C}$  nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 179.2 (broad), 178.0 (broad), 176.6 (broad), 176.0 (broad), 175.6 (broad) and 175.2 (broad).

37. The compound of claim 1 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 14.

38. The compound of claim 37 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 13.

39. The compound of claim 1 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having a chemical shift difference of 0.4 or 4.0 between the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance

40. The compound of claim 39 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having chemical shift differences of 0.4, 0.8, 1.4, 2.8 and 4.0 between the lowest ppm carbonyl carbon resonance and other carbonyl carbon resonances.

41. The compound of claim 1 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of  $70 \pm 2^\circ$  and  $97 \pm 2^\circ\text{C}$  obtained in an open cup at a heating rate of  $2^\circ\text{C}/\text{minute}$  under a nitrogen flow bubbled through  $15.3^\circ\text{C}$  water.

42. The compound of claim 41 characterized by a differential scanning calorimetry curve wherein the  $70 \pm 2^\circ\text{C}$  endotherm has an onset temperature of  $63 \pm 2^\circ\text{C}$ , and the  $97 \pm 2^\circ\text{C}$  endotherm has an onset temperature of  $87 \pm 2^\circ\text{C}$ .

43. The compound of claim 41 characterized by a differential scanning calorimetry curve having endotherms with peak temperatures of 70° and 97°C obtained in an open cup at a heating rate of 2°C/minute under a nitrogen flow bubbled through 15.3°C water.

5

44. The compound of claim 43 characterized by a differential scanning calorimetry curve wherein the 70°C endotherm has an onset temperature of 63°C, and the 97°C endotherm has an onset temperature of 87°C.

10

45. The compound of claim 1 characterized by the differential scanning calorimetry curve shown in Figure 11.

46. The compound of claim 1 having a thermogravimetry curve obtained under a nitrogen flow at a heating rate of 10°C/minute characterized by a 1.5% weight loss from ambient room temperature to an inflection point in the weight loss curve at about 50°C, followed by a 4.2% weight loss between about 50°C and a stable weight loss plateau at about 119°C.

47. The compound of claim 1 characterized by the thermogravimetry curve shown in Figure 12.

48. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 12.2° and 13.5°.

25

49. The compound of claim 48 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 12.17° and 13.50°.

30

50. The compound of claim 49 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 12.165° and 13.503°.

51. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values:

35

3.8°, 8.1°, 10.3°, 12.2°, 13.5°, 14.1°, 14.6°, 17.8°, 18.2° and 20.0°.

52. The compound of claim 1 characterized by solid-state  $^{13}\text{C}$  nuclear magnetic resonance having the following chemical shifts expressed in parts  
5 per million: 178.7, 178.3, 178.1, 177.7, 176.8 (broad), 176.2 and 175.2.

53. The compound of claim 52 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 17.

10 54. The compound of claim 53 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 16.

55. The compound of claim 1 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having a chemical shift difference of 1.0 or 3.5 between  
15 the lowest ppm carbonyl carbon resonance and another carbonyl carbon resonance.

56. The compound of claim 55 characterized by solid state  $^{13}\text{C}$  nuclear magnetic resonance having chemical shift differences of 1.0, 1.6, 2.5, 2.9, 3.1 and 3.5 between the lowest ppm carbonyl carbon resonance and other carbonyl carbon  
20 resonances.

57. The compound of claim 1 having an x-ray powder diffraction pattern obtained using  $\text{CuK}\alpha$  radiation containing the following angle 2 theta values: 9.0° and 11.8°.  
25

58. The compound of claim 57 having an x-ray powder diffraction pattern obtained using  $\text{CuK}\alpha$  radiation containing the following angle 2 theta values: 9.04° and 11.78°.

30 59. The compound of claim 58 having an x-ray powder diffraction pattern obtained using  $\text{CuK}\alpha$  radiation containing the following angle 2 theta values: 9.042° and 11.779°.

60. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 9.0°, 10.3°, 11.8°, 12.9°, 13.2°, 14.1°, 14.9°, 16.7°, 16.9°, 17.8°, 19.1°, 19.4°, 19.7° and 20.5°.

5

61. The compound of claim 1 characterized by a differential scanning calorimetry curve having an endotherm with peak temperature of 89  $\pm$ 2° obtained in an open cup at a heating rate of 2°C/minute under a nitrogen flow bubbled through -1.0°C water.

10

62. The compound of claim 61 characterized by a differential scanning calorimetry curve wherein the 89  $\pm$ 2°C endotherm has an onset temperature of 76  $\pm$ 2°C.

15

63. The compound of claim 61 characterized by a differential scanning calorimetry curve having an endotherm with peak temperature of 89°C obtained in an open cup at a heating rate of 2°C/minute under a nitrogen flow bubbled through -1.0°C water.

20

64. The compound of claim 63 characterized by a differential scanning calorimetry curve wherein the 89 °C endotherm has an onset temperature of 76 °C.

25

65. The compound of claim 1 characterized by the differential scanning calorimetry curve shown in Figure 19.

30

66. The compound of claim 1 having a thermogravimetry curve obtained under a nitrogen flow at a heating rate of 10°C/minute characterized by a 1.2% weight loss from ambient room temperature to an inflection point in the weight loss curve at about 47°C, followed by a 0.7% weight loss between about 47°C and a stable weight loss plateau at about 100°C.

35

67. The compound of claim 1 characterized by the thermogravimetry curve shown in Figure 20.

68. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 6.7° and 13.4°.

5 69. The compound of claim 68 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 6.69° and 13.42°.

70. The compound of claim 69 having an x-ray powder diffraction  
10 pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 6.693° and 13.424°.

71. The compound of claim 1 having an x-ray powder diffraction  
15 pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 2.9°, 3.6°, 6.7°, 7.3°, 10.2°, 13.4° and 14.6°.

72. The compound of claim 1 characterized by a differential  
scanning calorimetry curve showing no observable major thermal event up to a final  
analysis temperature of about 120°C obtained in an open cup at a heating rate of  
20 2°C/minute under a nitrogen flow bubbled through -1.0°C water.

73. The compound of claim 1 characterized by the differential  
scanning calorimetry curve shown in Figure 22.

25 74. The compound of claim 1 having a thermogravimetry curve obtained under a nitrogen flow at a heating rate of 10°C/minute characterized by a 2.5% weight loss from ambient room temperature up to a stable weight loss plateau at about 92°C.

30 75. The compound of claim 1 characterized by the thermogravimetry curve shown in Figure 23.

76. The compound of claim 1 having an x-ray powder diffraction  
pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values:  
35 3.1° and 3.6°.

- 5 77. The compound of claim 76 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 3.13° and 3.62°.
78. The compound of claim 77 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 3.127° and 3.620°.
- 10 79. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK $\alpha$  radiation containing the following angle 2 theta values: 3.1°, 3.6, 6.5° and 7.2°.
- 15 80. The compound of claim 1 characterized by an x-ray powder diffraction pattern having an angle 2 theta value in a range from 3.5 to 3.8° obtained with Cu K $\alpha$  radiation at an accelerating potential of 45 kV and a current of 40 mA from 2° to 23° 2 theta with a step size of 0.015° and a collection time of 1.80 seconds per step.
- 20 81. The compound of claim 1 characterized by differential scanning calorimetry as having endotherms with peak temperatures of 222  $\pm$ 2°C and 241  $\pm$ 2°C obtained in an open cup at a heating rate of 10°C/minute under a nitrogen flow bubbled through water at 16.0°C.
- 25 82. The compound of claim 1 characterized by differential scanning calorimetry as having an endotherm with a peak temperature of 201  $\pm$ 2°C obtained in an open cup at a heating rate of 2°C/minute under a nitrogen flow bubbled through water at 19.0°C.
- 30 83. A method of inhibiting HMG-CoA reductase comprising administering to a patient in need of such treatment an effective inhibitory amount of the compound of claim 1.

84. A method of inhibiting HMG-CoA reductase comprising administering to a patient in need of such treatment an effective inhibitory amount of the compound of claim 2.

5 85. A method of treating hypercholesterolemia comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of claim 1.

10 86. The method of claim 85 wherein the compound is administered orally.

87. The method of claim 86 wherein the compound is administered in a delayed-release pharmaceutical dosage form.

15 88. The method of claim 87 wherein the delayed-release pharmaceutical dosage form is an enteric coated pharmaceutical dosage form.

89. The method of claim 86 wherein the compound is administered in a time controlled-release pharmaceutical dosage form.

20 90. The method of claim 86 wherein the compound is administered in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

25 (i) a therapeutically effective amount of the compound; and  
(ii) a polymer which upon hydration forms gelatinous microscopic particles; and

30 (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

91. A method of treating hypercholesterolemia comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of claim 2.

5 92. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 1 to a person at risk of developing atherosclerotic disease.

10 93. The method of Claim 92 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

15 94. The method of Claim 93 wherein the cardiovascular disease is coronary heart disease.

20 95. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 2 to a person at risk of developing atherosclerotic disease.

25 96. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 1 to a person who has atherosclerotic disease.

97. The method of Claim 96 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

30 98. The method of Claim 97 wherein the cardiovascular disease is coronary heart disease.

35 99. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person who has atherosclerotic disease.

100. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount the compound of claim 1 to a person at risk of having an atherosclerotic disease event.

5

101. The method of Claim 100 wherein the person receiving the compound has atherosclerotic disease.

102. The method of Claim 100 wherein the person receiving the compound is at risk of developing atherosclerotic disease.

10

103. The method of Claim 100 wherein the atherosclerotic disease event is selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.

15

104. The method of Claim 103 wherein the coronary heart disease event is selected from coronary heart disease death, myocardial infarction, and coronary revascularization procedures.

20

105. The method of Claim 103 wherein the cerebrovascular event is selected from a cerebrovascular accident and a transient ischemic attack.

106. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person at risk of having an atherosclerotic disease event.

25

107. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

30

108. The pharmaceutical composition of claim 107 formulated for oral administration.

109. The pharmaceutical composition of claim 108 formulated in a delayed-release dosage form wherein release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

5 110. The pharmaceutical composition of claim 109 wherein the dosage form has an enteric coating.

111. The pharmaceutical composition of claim 108 formulated in a time controlled-release dosage form.

10

112. The pharmaceutical composition of claim 108 formulated in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

15 (i) a therapeutically effective amount of the compound; and  
(ii) a polymer which upon hydration forms gelatinous microscopic particles; and

(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of  
20 the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

25 113. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier.

114. A process for preparing a pharmaceutical composition comprising combining the compound of claim 1 with a pharmaceutically acceptable  
30 carrier.

115. A process for preparing a pharmaceutical composition comprising combining the compound of claim 2 with a pharmaceutically acceptable carrier.

35

116. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

5 117. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier.

10 118. A process for making the compound of claim 2 comprising the steps of:

A) combining a mixture of a salt of dihydroxy open acid simvastatin in an aqueous solvent with calcium acetate hydrate to form an amorphous calcium salt of dihydroxy open acid simvastatin, wherein the aqueous solvent is selected from water, an aqueous-protic organic solvent mixture and an aqueous-aprotic organic solvent mixture;

B) aging the resulting mixture at a temperature up to 50°C until turnover of the amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline calcium salt of dihydroxy open acid simvastatin is complete;

C) recovering the crystalline calcium salt of dihydroxy open acid simvastatin; and

D) drying the recovered crystals under a moist atmosphere.

119. The process of claim 118 wherein all the steps are performed under an inert atmosphere.

120. The process of claim 118 wherein the protic organic solvent is selected from the group consisting of ethanol, methanol, isopropyl alcohol and n-propyl alcohol, and the aprotic solvent is selected from the group consisting of acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide and tetrahydrofuran, *tert*-butyl methyl ether and toluene.

121. The process of claim 118 wherein the protic organic solvent is selected from the group consisting of ethanol, methanol, isopropyl alcohol and n-propyl alcohol, and the aprotic solvent is selected from the group consisting of tetrahydrofuran, *tert*-butyl methyl ether and toluene.

122. The process of claim 118 wherein the protic organic solvent is selected from the group consisting of ethanol and n-propyl alcohol.
- 5 123. The process of claim 118 wherein the aqueous solvent is an aqueous n-propyl alcohol mixture.
- 10 124.. The process of claim 118 wherein in step (A), the salt of dihydroxy open acid simvastatin is a metal salt, and the pH of the mixture of the salt of dihydroxy open acid simvastatin in an aqueous solvent is adjusted to 6 to 11 prior to combining it with the calcium acetate hydrate.
125. The process of claim 124 wherein the pH is adjusted to 6 to 9.
- 15 126. The process of claim 124 wherein the pH is adjusted to 7 to 8.5.
127. The process of claim 124 wherein the pH is adjusted by addition to the mixture of an acid selected from a mineral acid and acetic acid.
- 20 128. The process of claim 127 wherein the pH is adjusted by addition to the mixture of a mineral acid.
- 25 129. The process of claim 118 wherein in step (A), the salt of dihydroxy open acid simvastatin is the ammonium salt.
130. The process of claim 118 wherein in step (A), the calcium acetate hydrate is added in portions to the mixture of the salt of dihydroxy open acid simvastatin.
- 30 131. The process of claim 118 wherein in step (B), the mixture is aged at a temperature from about 10°C to 50°C.
- 35 132. The process of claim 131 wherein in step (B), the mixture is aged at a temperature from room temperature to 50°C.

133. The process of claim 132 wherein in step (B), the mixture is aged at a temperature from about 30°C to 40°C.

5 134. The process of claim 133 wherein in step (B), the mixture is aged at a temperature from about 30°C to 35°C.

135. The process of claim 118 wherein in step (B), the resulting mixture is aged in the presence of seed.

10 136. The process of claim 118 wherein in steps (C) and (D), the crystalline calcium salt of dihydroxy open acid simvastatin is recovered by suction filtration and the recovered crystals are suction dried under a moist atmosphere, respectively.

15 137. The process of claim 118 wherein in step (D), the recovered crystals are dried under an inert moist atmosphere.

20 138. The process of claim 118 wherein in step (D), the recovered crystals are dried under an inert moist atmosphere at a temperature in the range from 10 to 40°C.

25 139. The process of claim 118 wherein in step (D), the recovered crystals are dried under an inert moist atmosphere at a temperature in the range from 25 to 35°C.

140. The process of claim 118 wherein in step (D), the moist atmosphere is an inert atmosphere having a relative humidity of 30 to 70%.

30 141. The process of claim 118 wherein in step (D), the moist atmosphere is an inert atmosphere having a relative humidity of 40 to 70%.

35 142. The process of claim 118 wherein in step (A), an anti-oxidant is combined with the salt of dihydroxy open acid simvastatin and the calcium acetate hydrate in the aqueous solvent.

143. The process of claim 118 wherein the anti-oxidant is selected from BHA, propyl gallate and combinations thereof.

144. The process of claim 142 wherein all the steps are performed  
5 under an inert atmosphere.

145. The process of claim 118 wherein in step (B), an anti-oxidant is combined with the mixture.

10 146. The process of claim 145 wherein the anti-oxidant is selected from BHA, propyl gallate and combinations thereof.

147. The process of claim 145 wherein all the steps are performed under an inert atmosphere.  
15

148. The process of claim 118 wherein in step (C), an anti-oxidant is combined with the recovered calcium salt of dihydroxy open acid simvastatin.

149. The process of claim 148 wherein the anti-oxidant is selected  
20 from BHA, propyl gallate and combinations thereof.

150. The process of claim 148 wherein all the steps are performed under an inert atmosphere.

25 151. The product produced from the process of claim 118.

152. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 36 and a pharmaceutically acceptable carrier.  
30

153. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 52 and a pharmaceutically acceptable carrier.

154. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 61 and a pharmaceutically acceptable carrier.

5 155. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 72 and a pharmaceutically acceptable carrier.

10 156. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 80 and a pharmaceutically acceptable carrier.

15 157. The compound of claim 1 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 25.

158. The compound of claim 157 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 24.

20 159. The compound of claim 1 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 27.

160. The compound of claim 159 characterized by the solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum shown in Figure 26.

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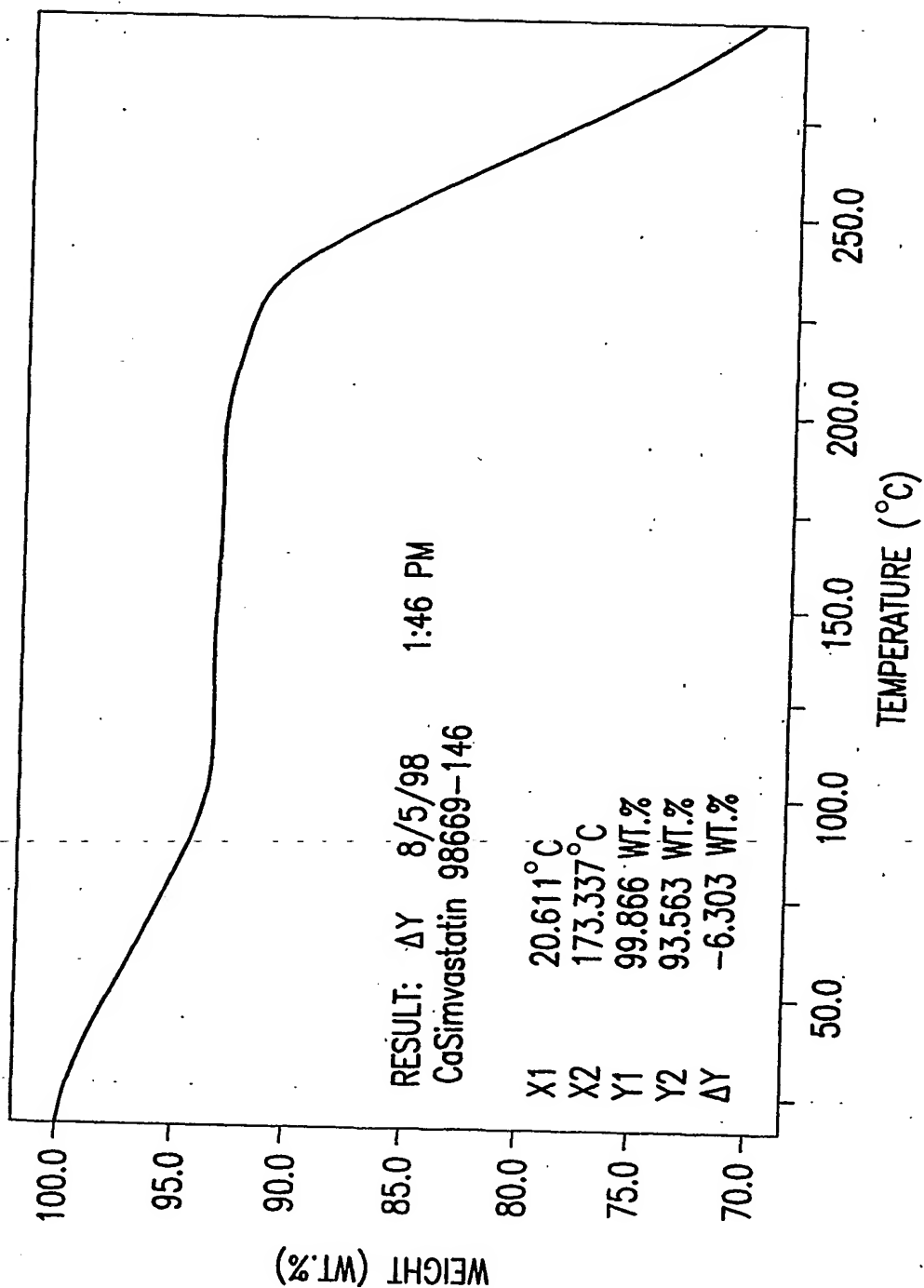


FIG.1

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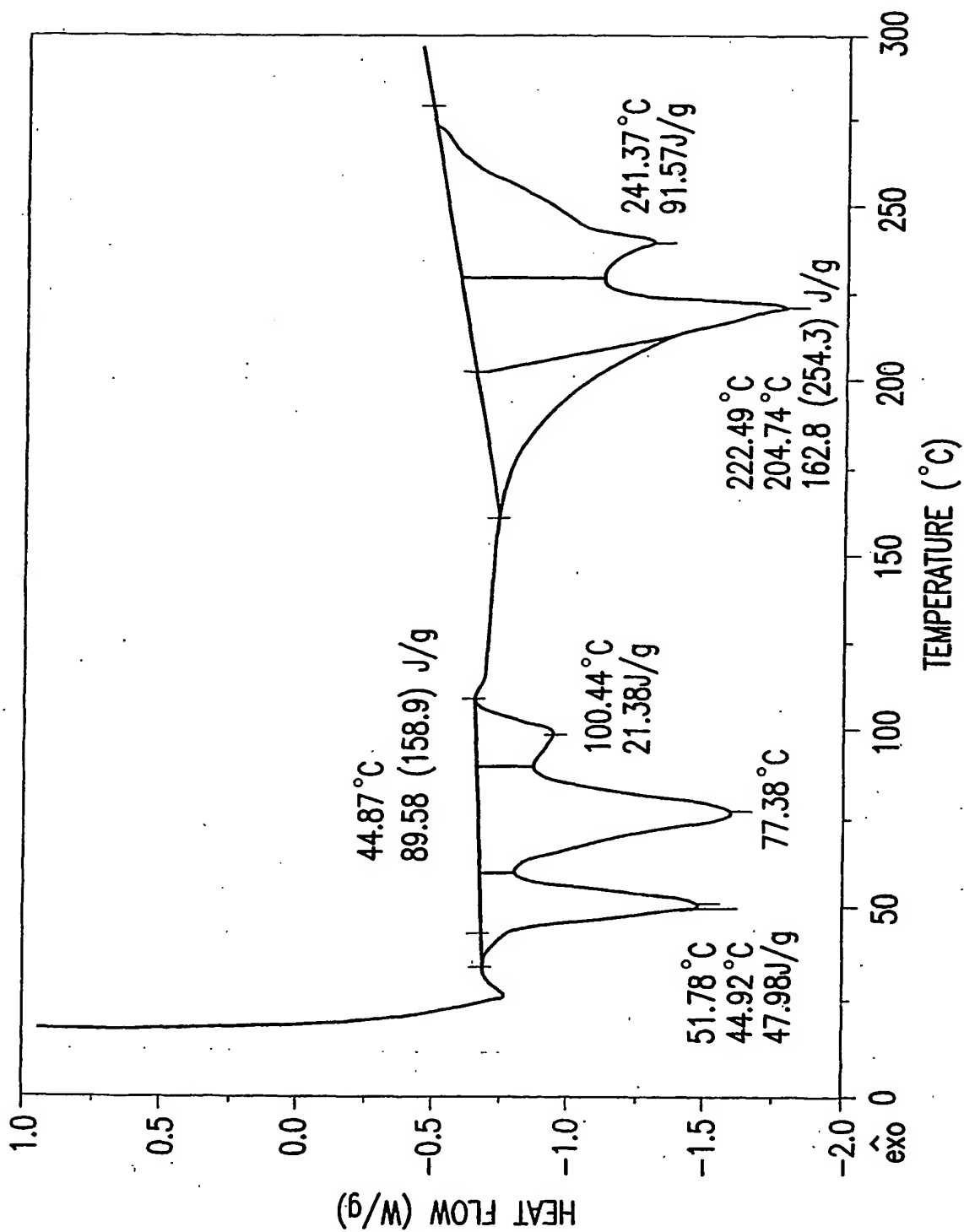


FIG. 2

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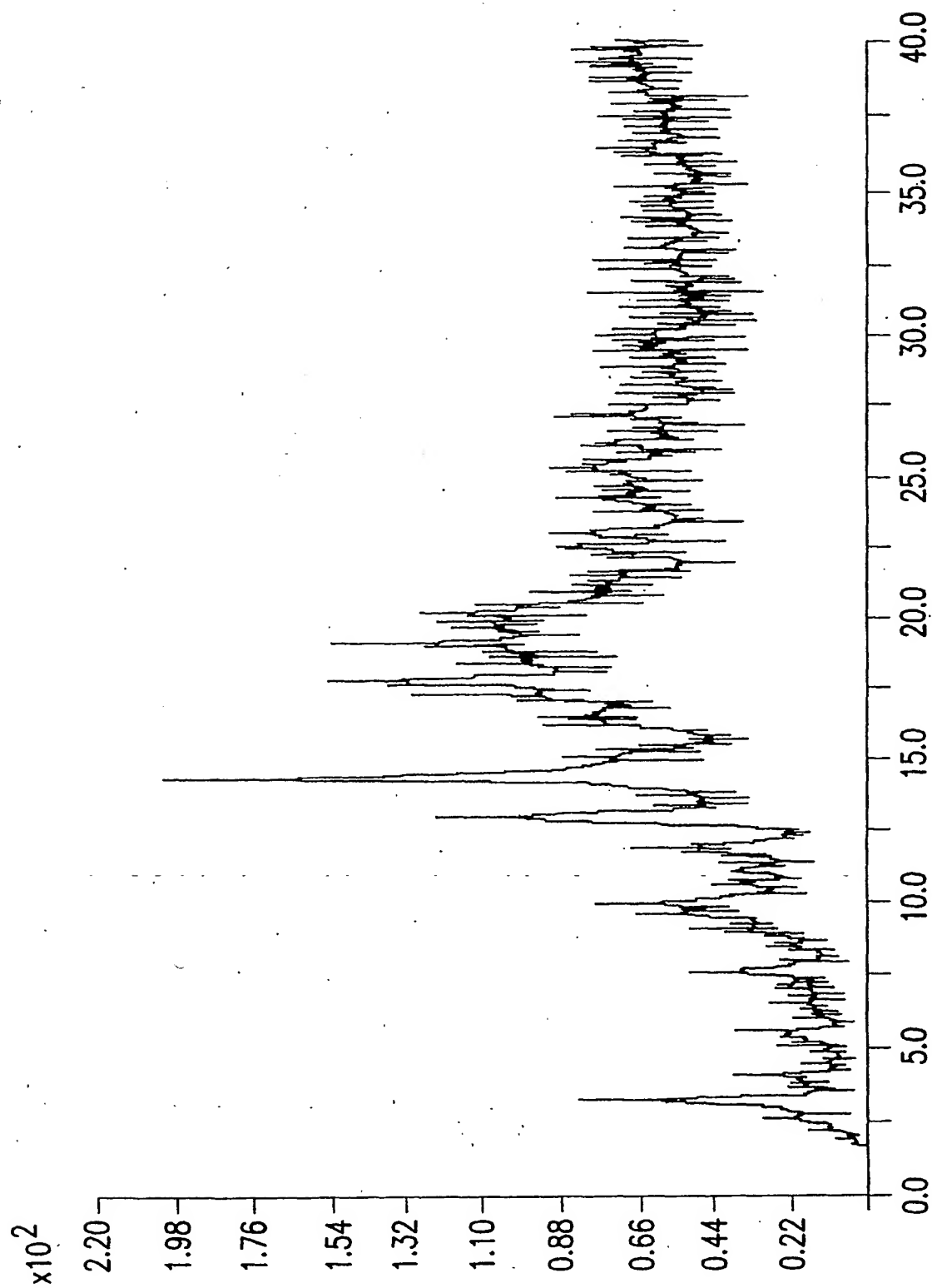


FIG.3

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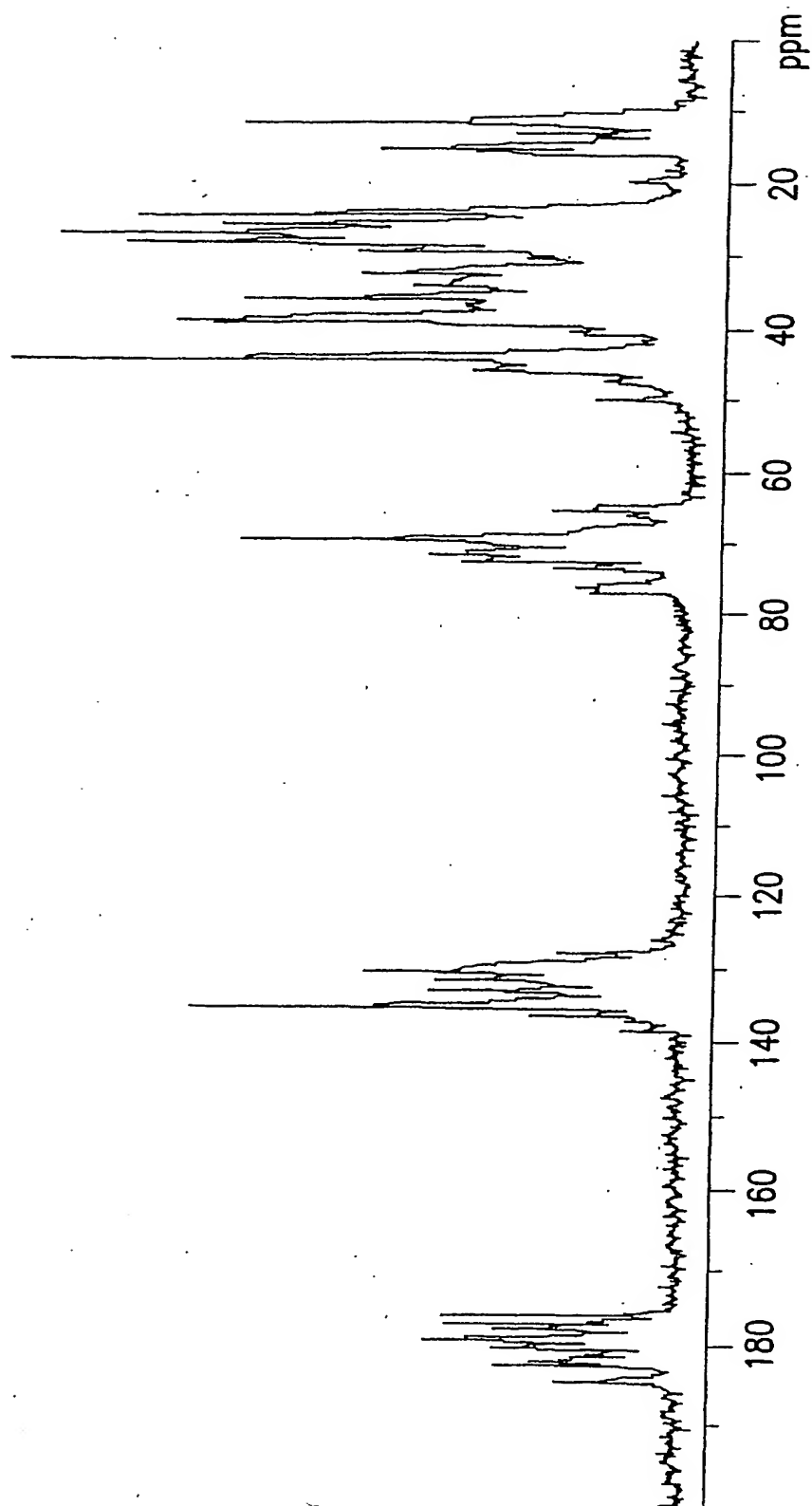


FIG.4

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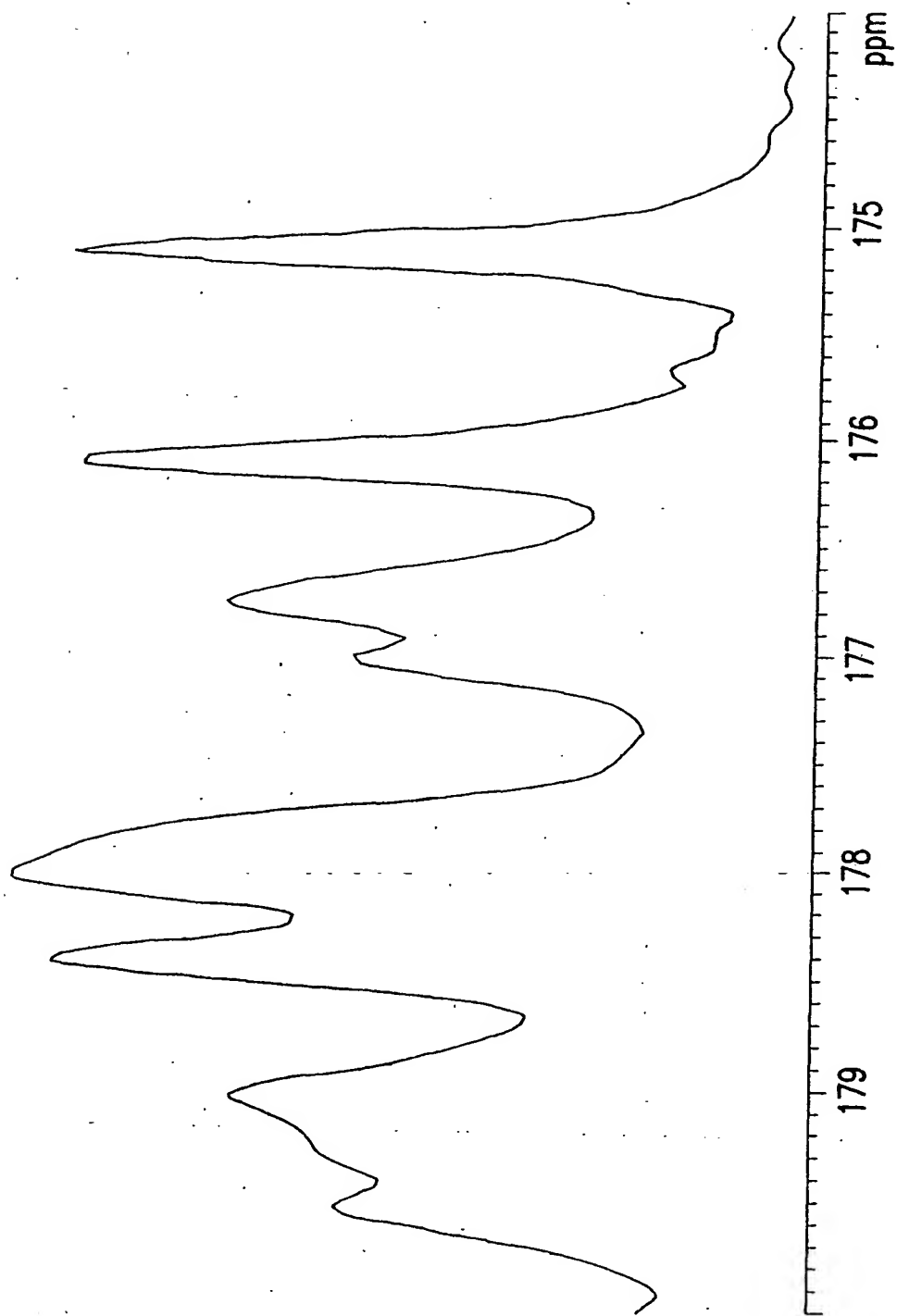
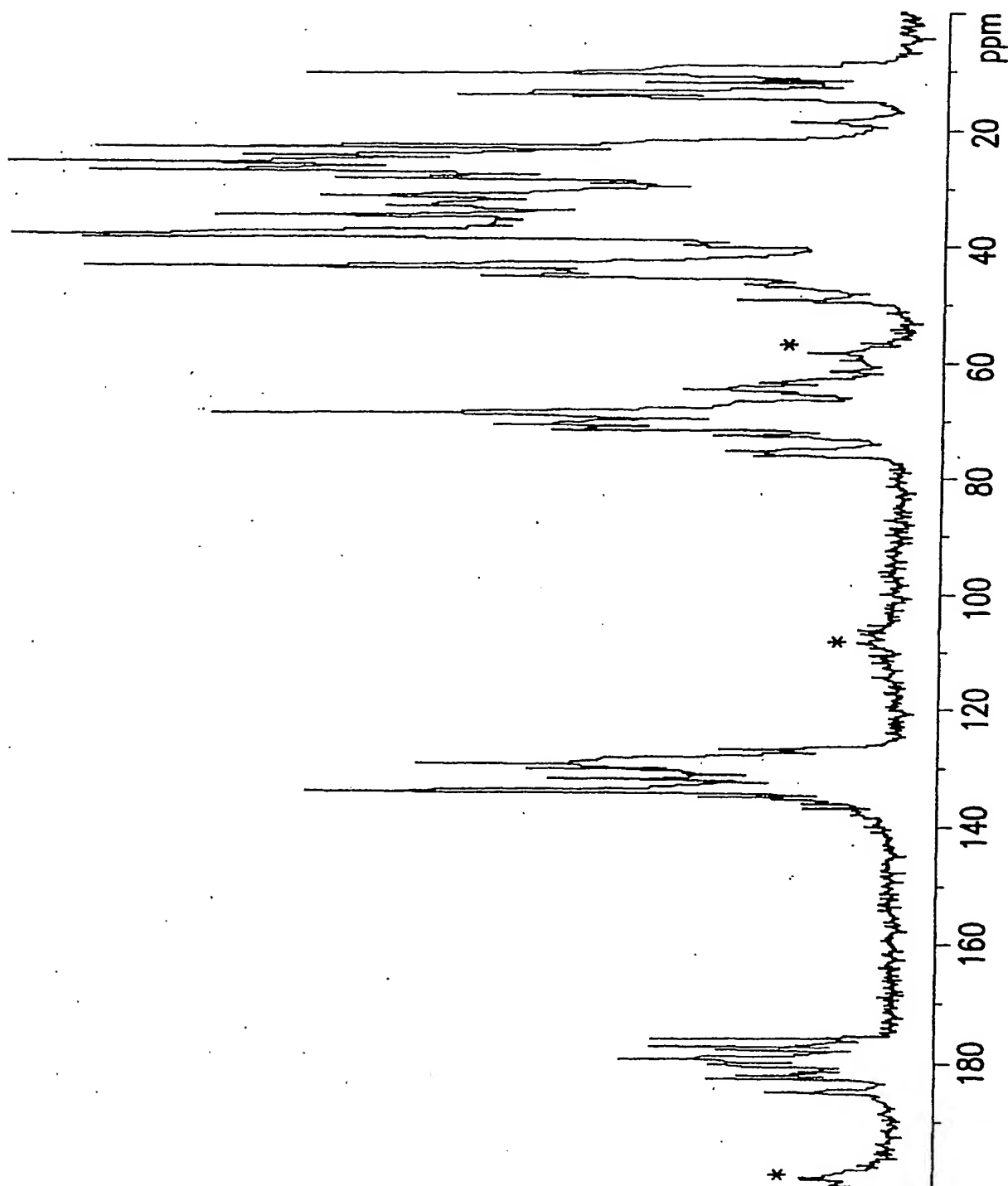


FIG.5

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FIG. 6



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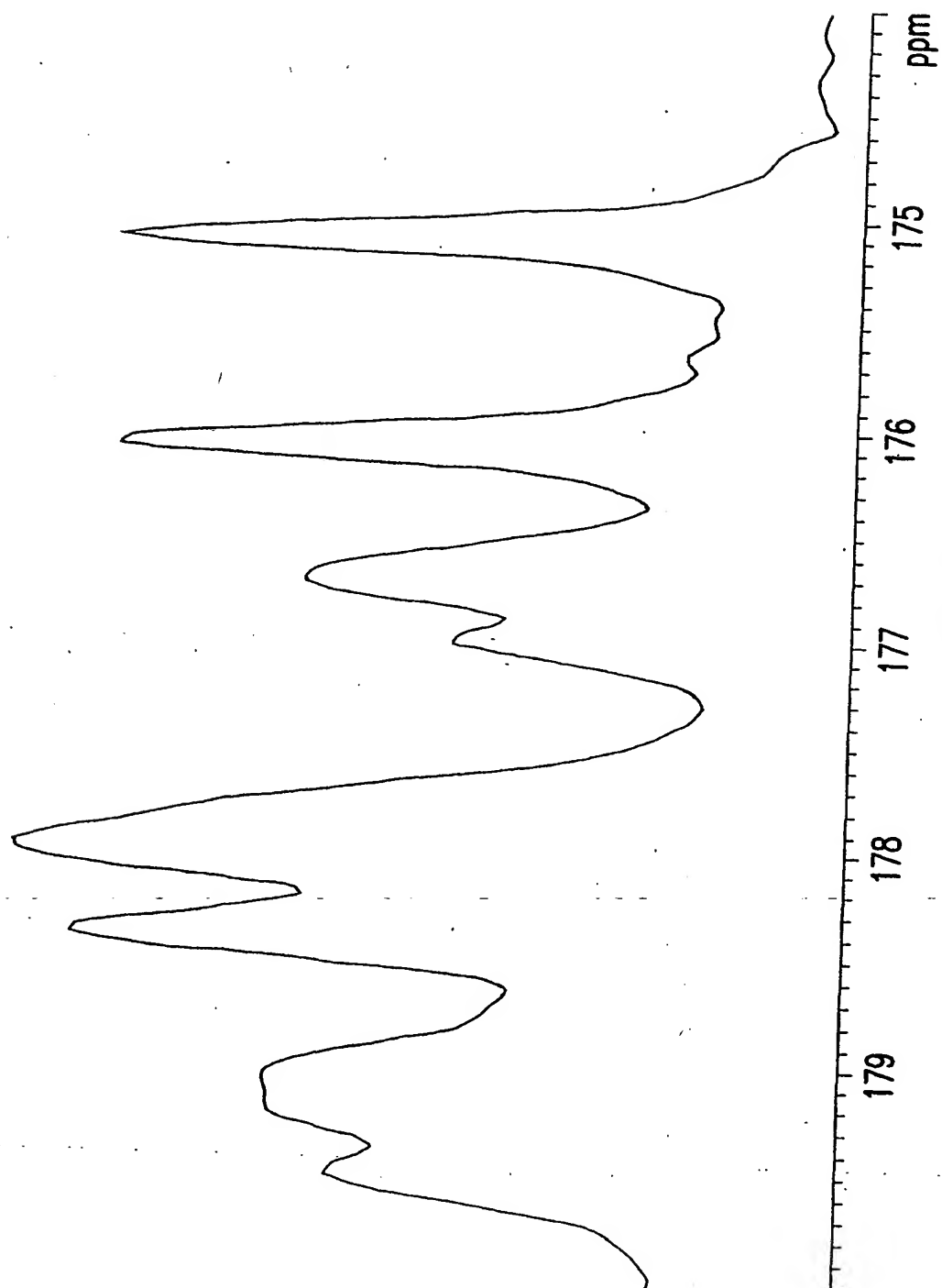


FIG.7

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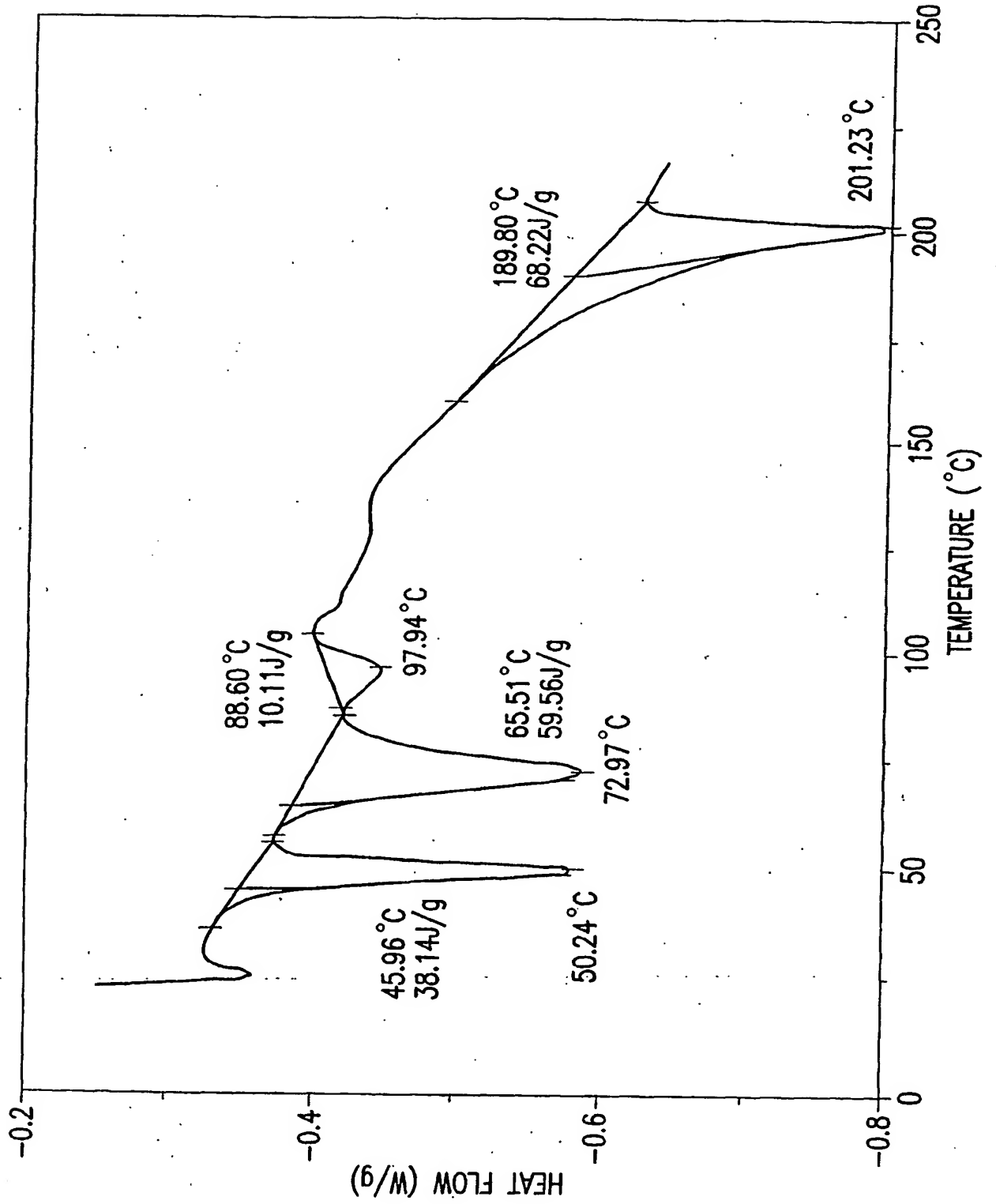


FIG. 8

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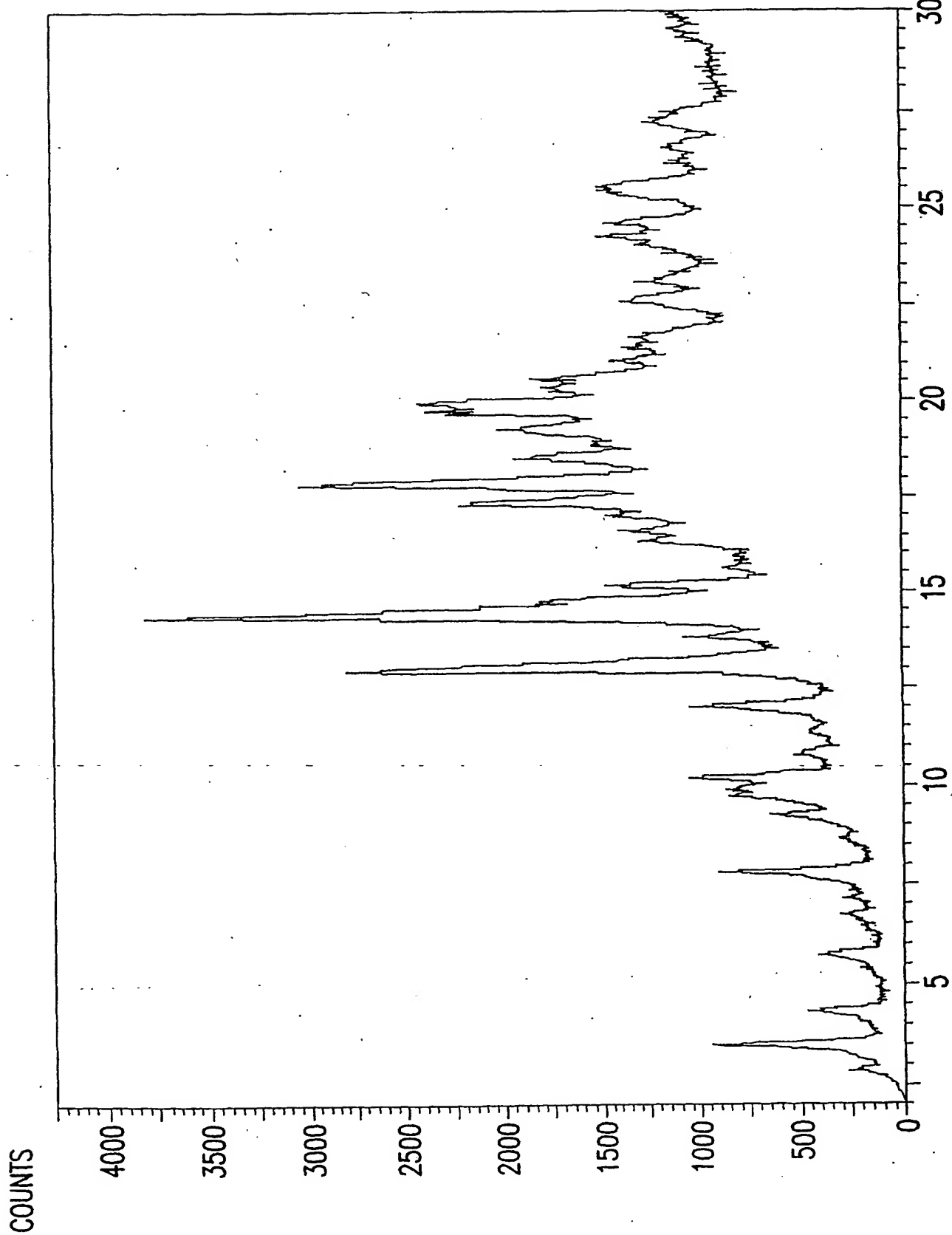
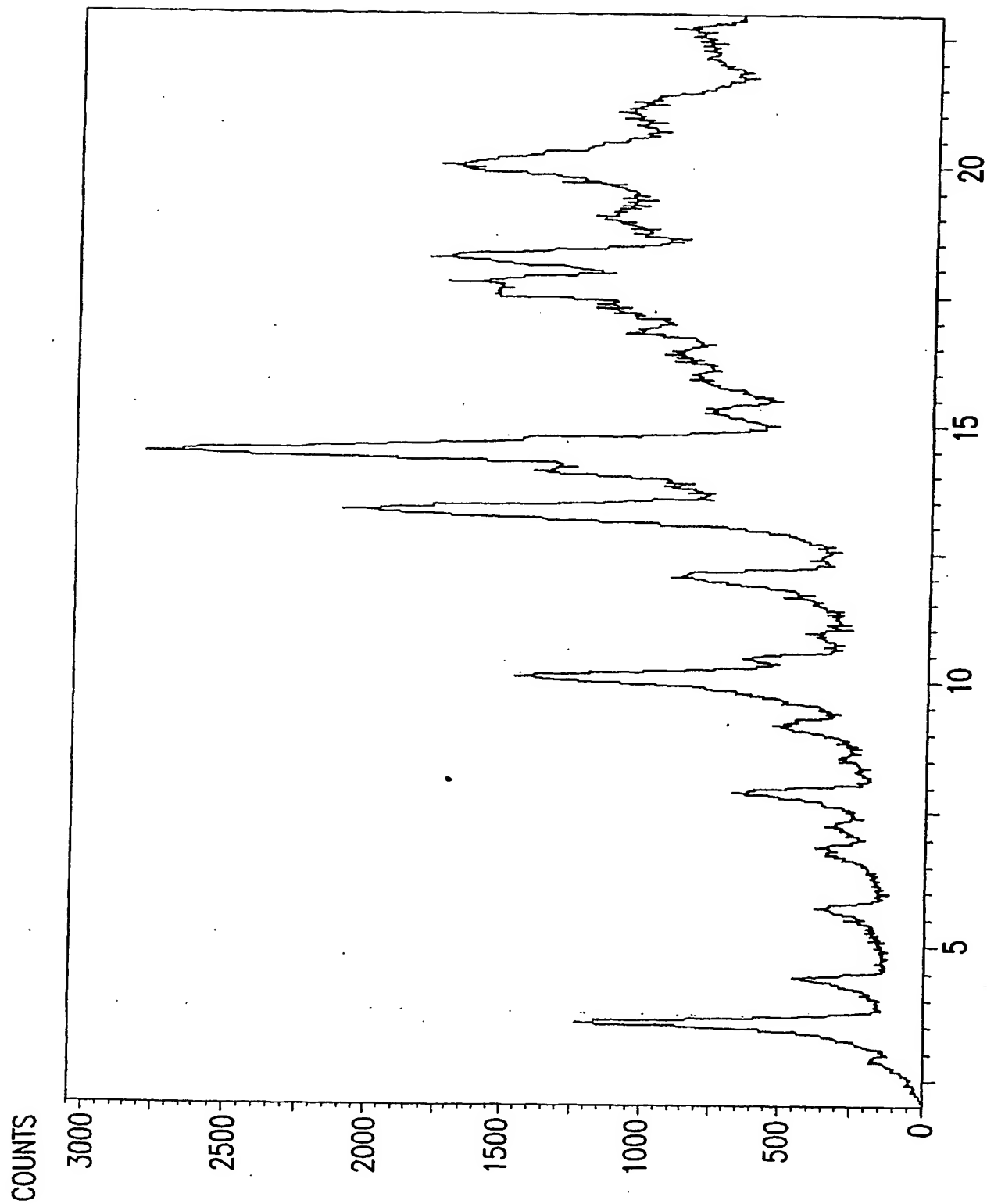


FIG. 9

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FIG. 10



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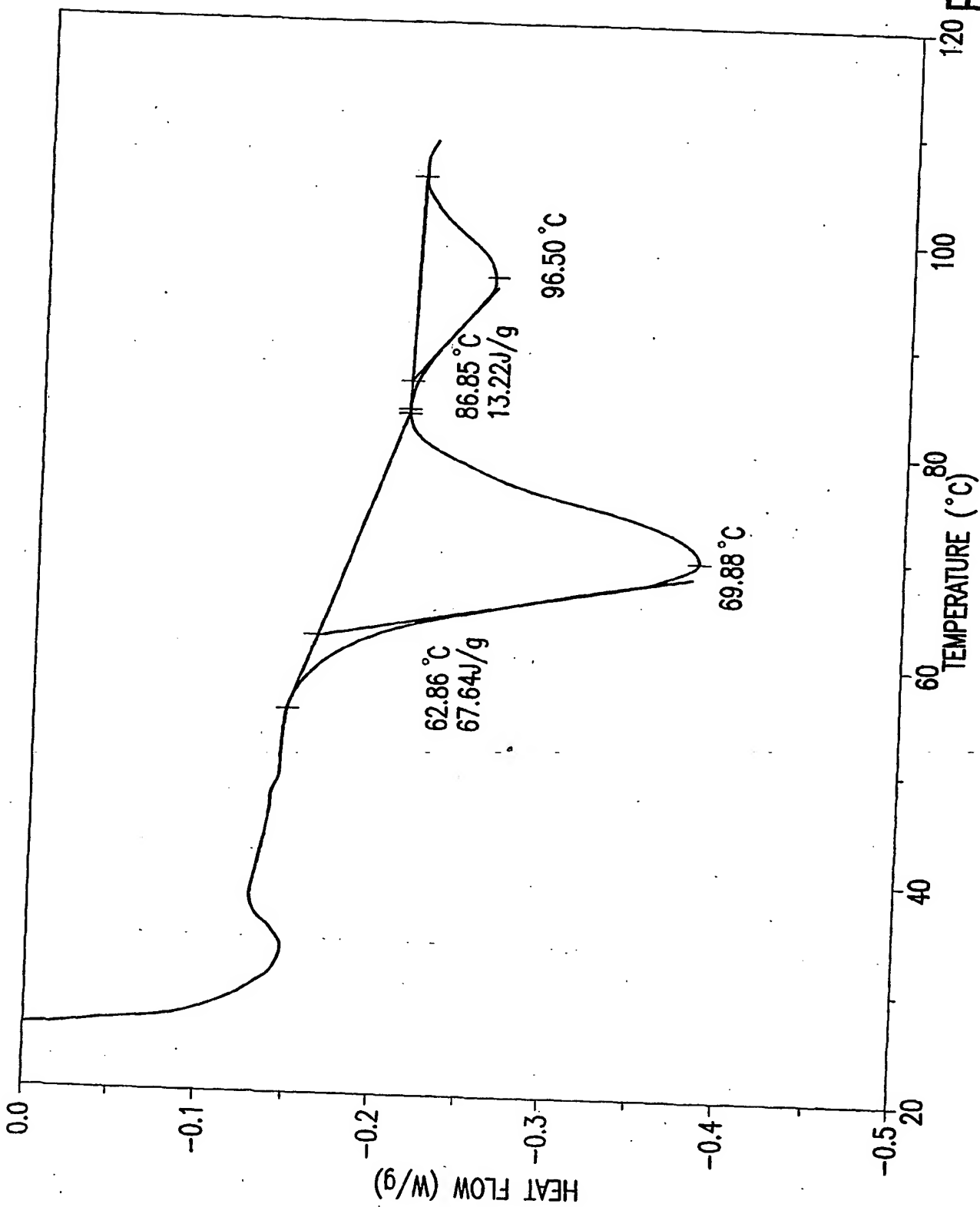


FIG. 11

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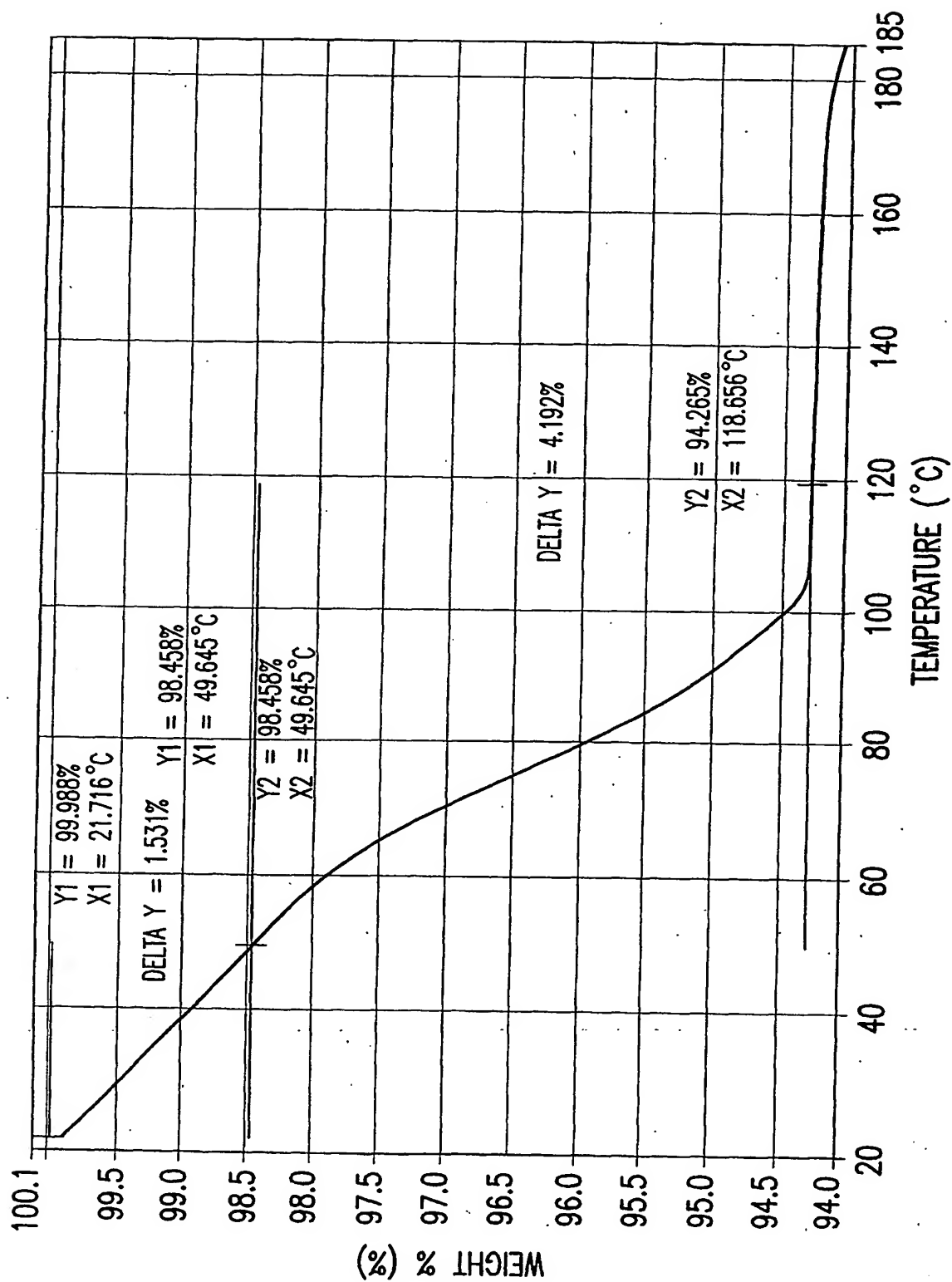
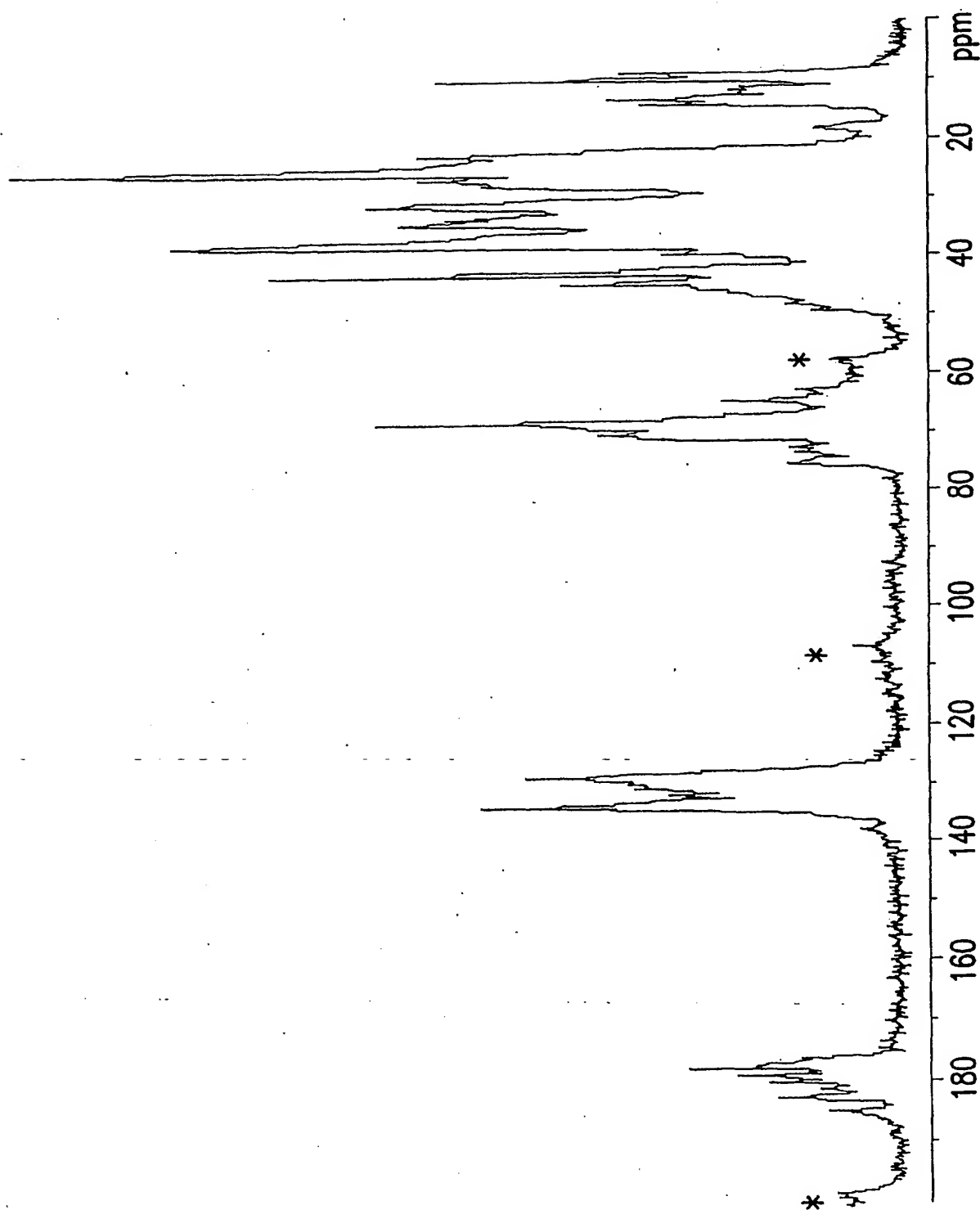


FIG. 12

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FIG. 13



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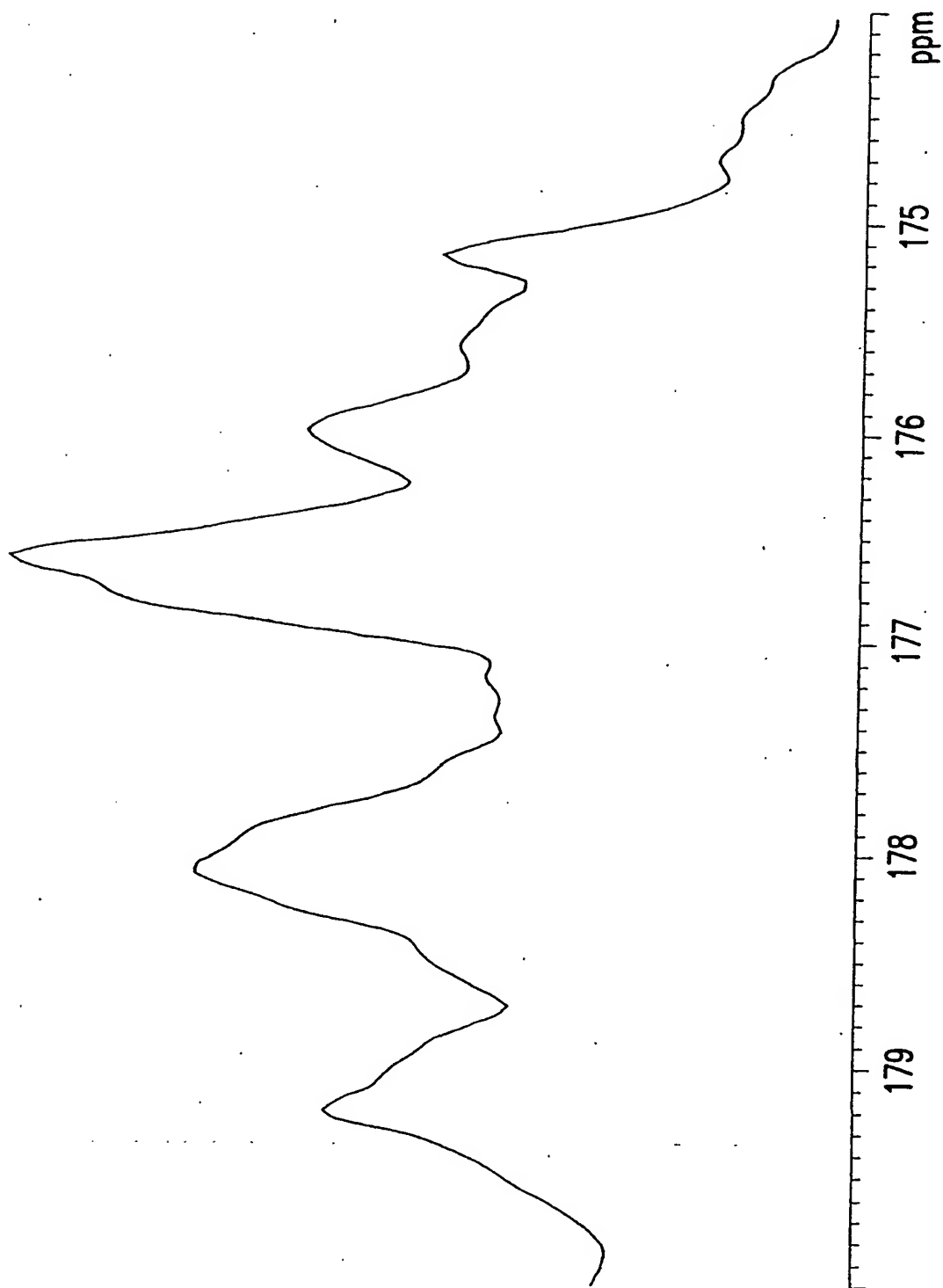


FIG. 14

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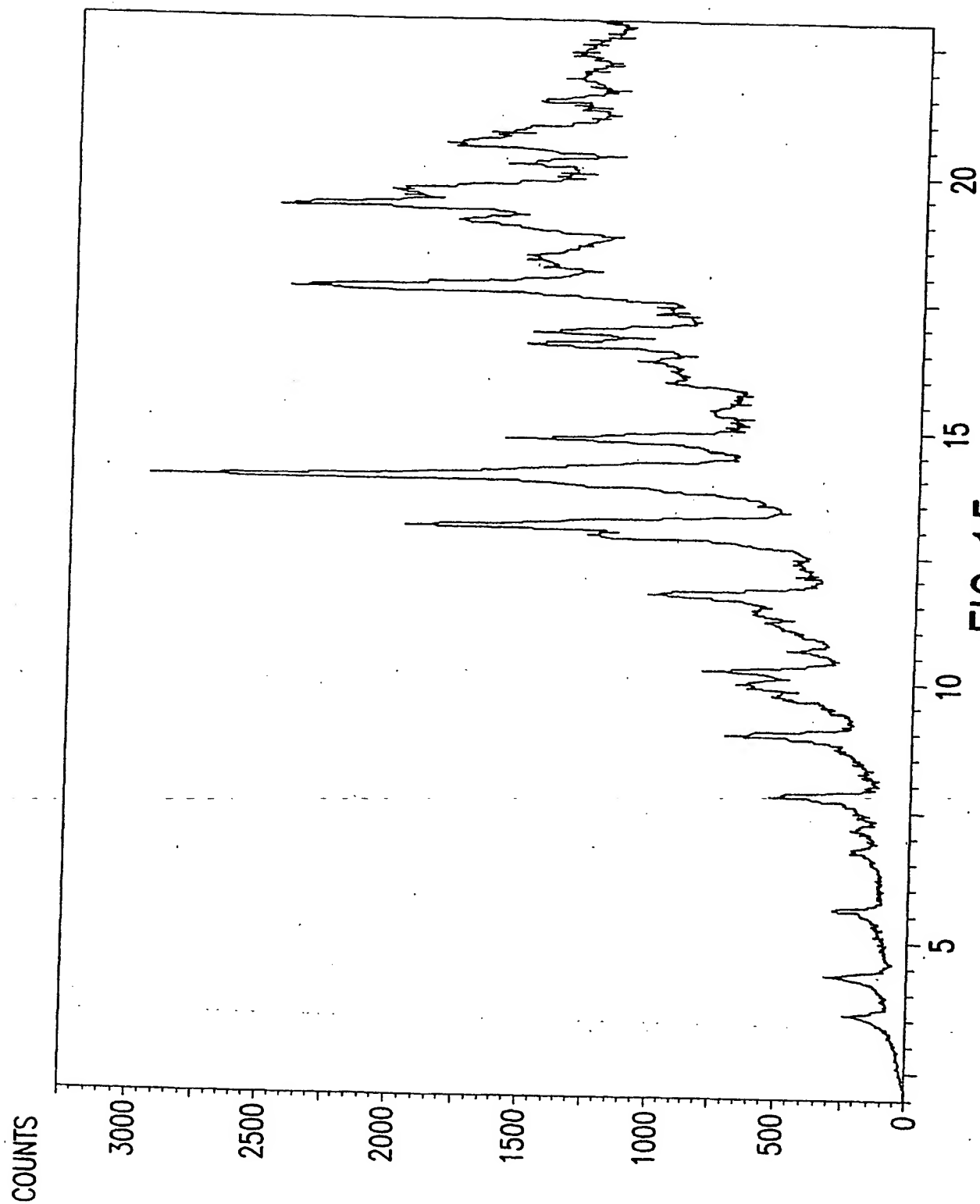
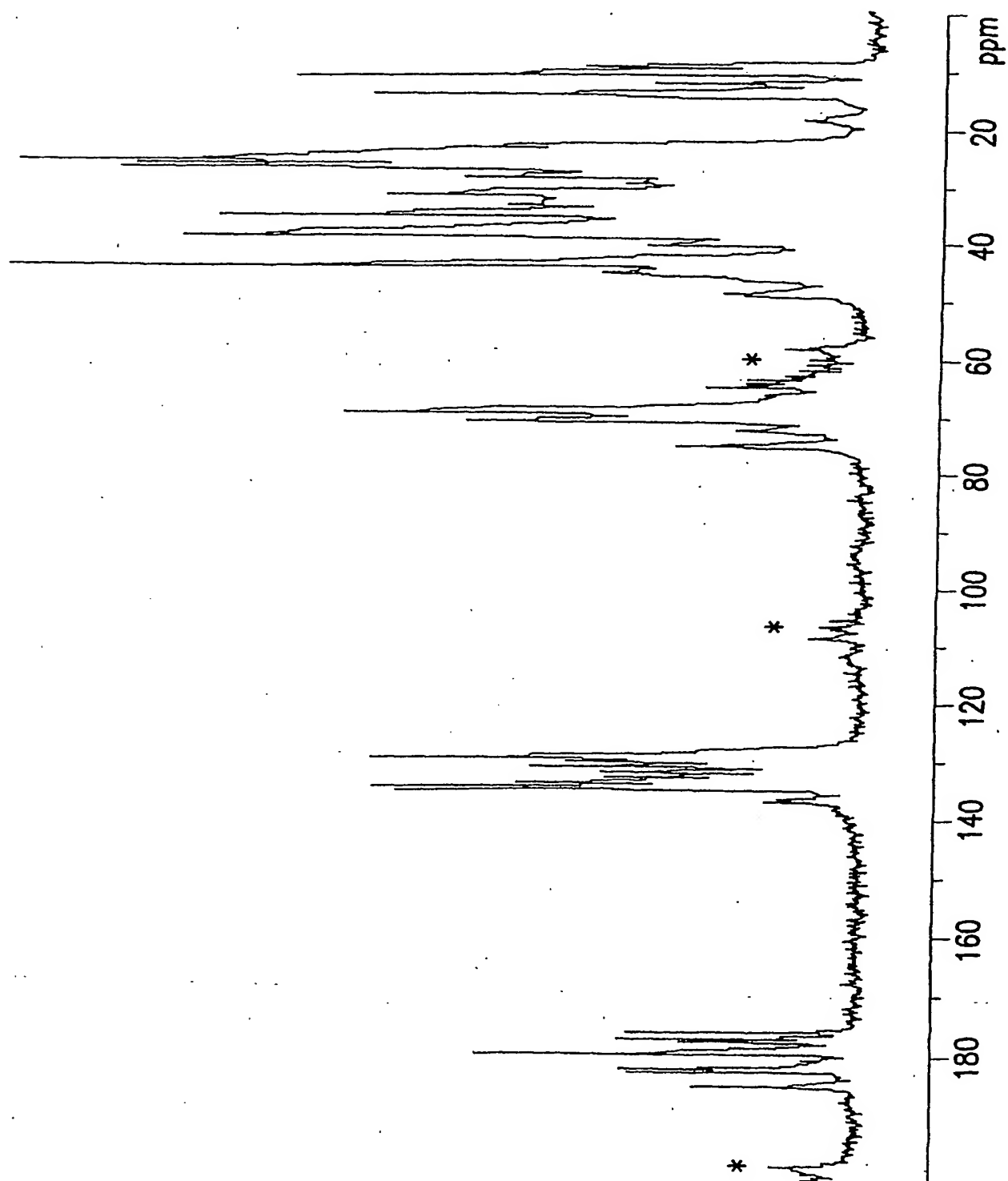


FIG. 15

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FIG. 16



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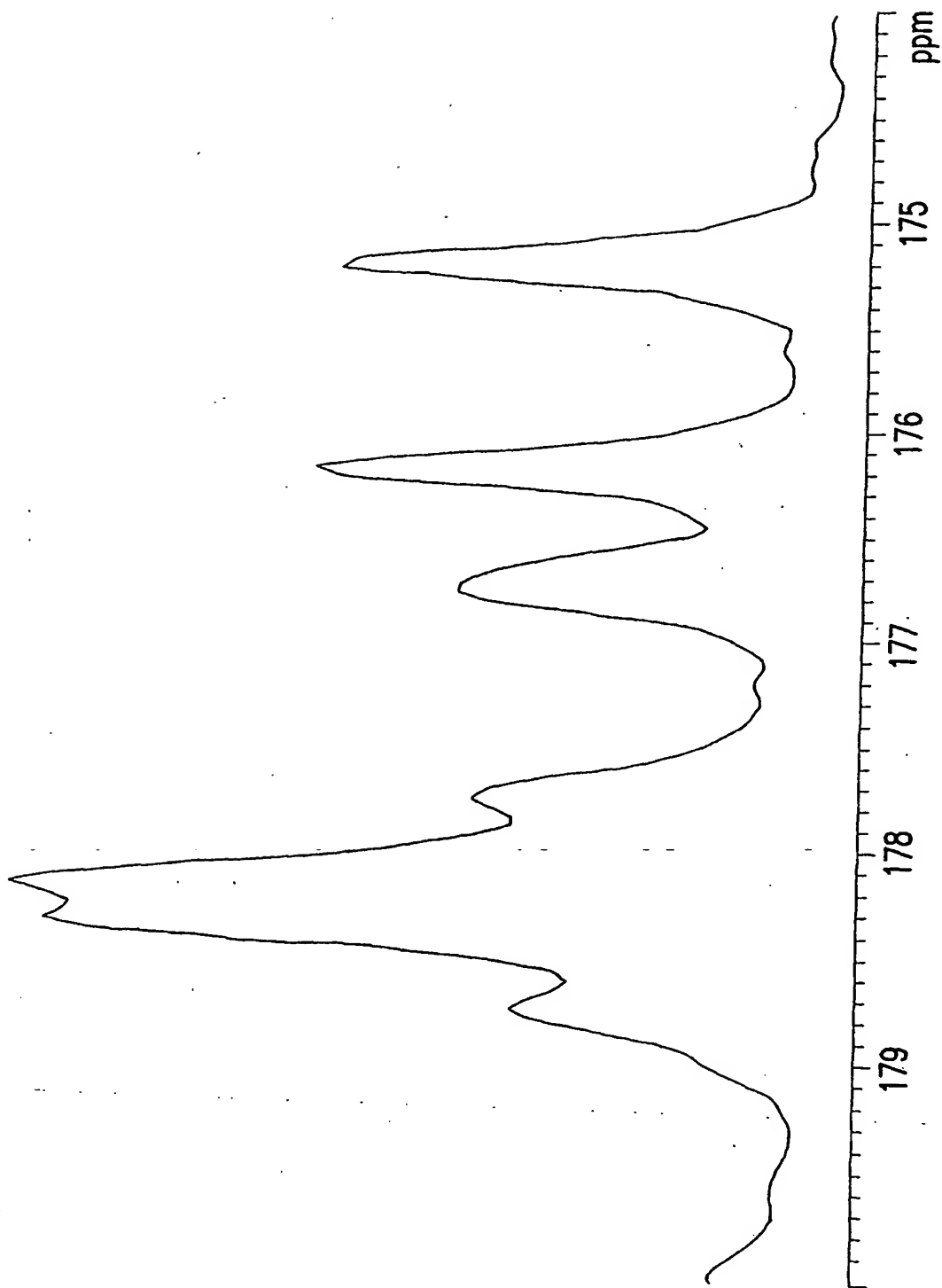
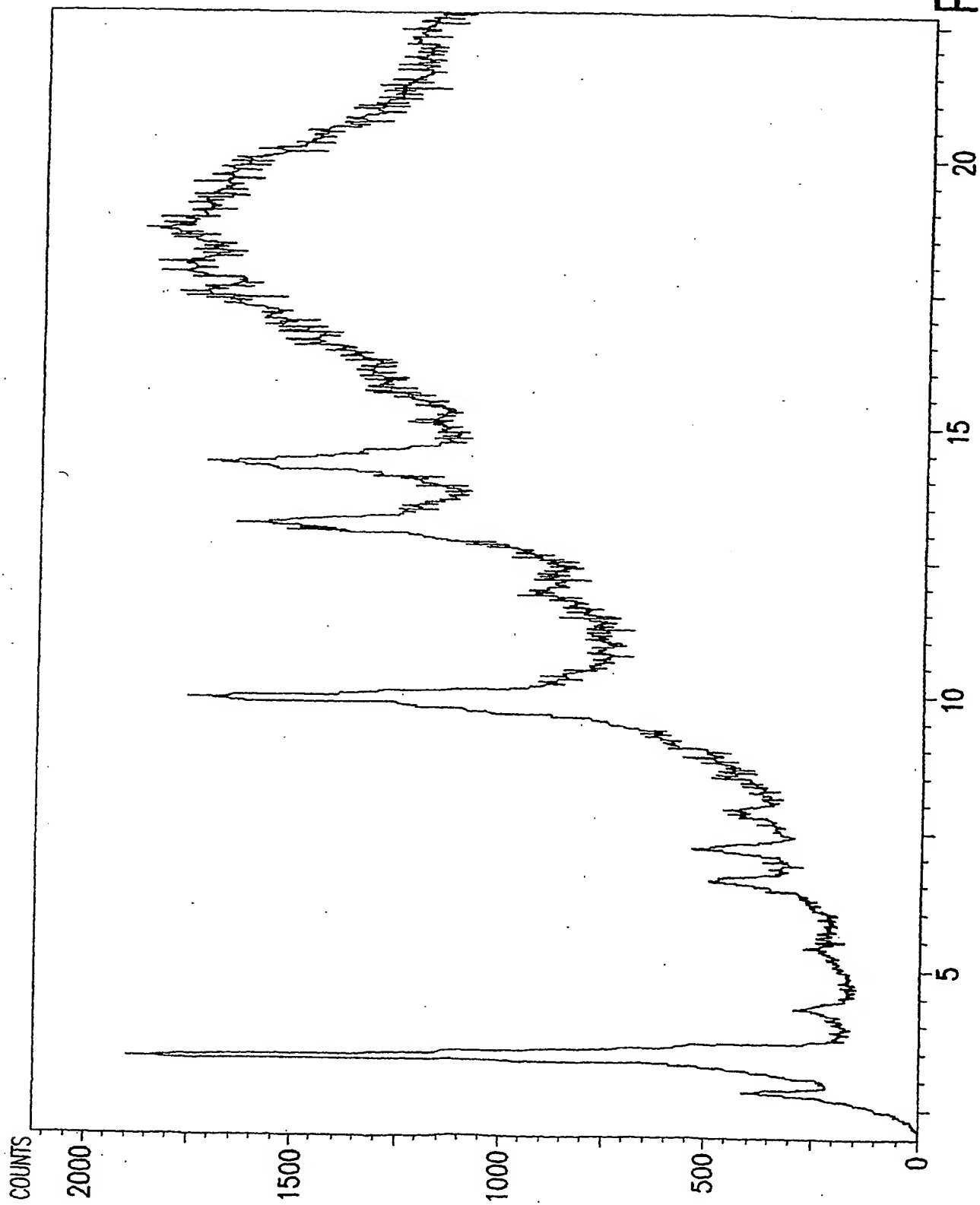


FIG. 17

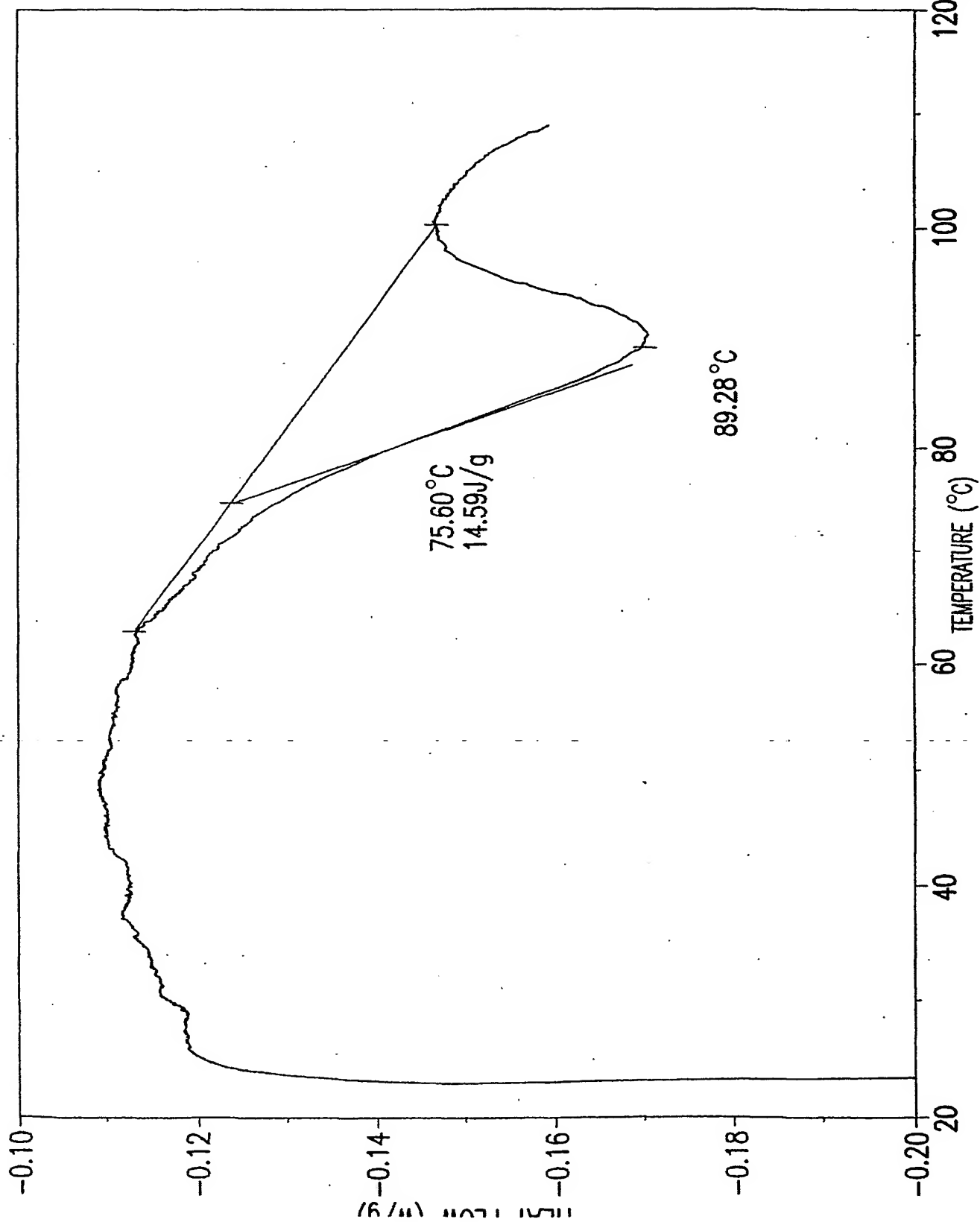
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FIG. 18



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FIG. 19



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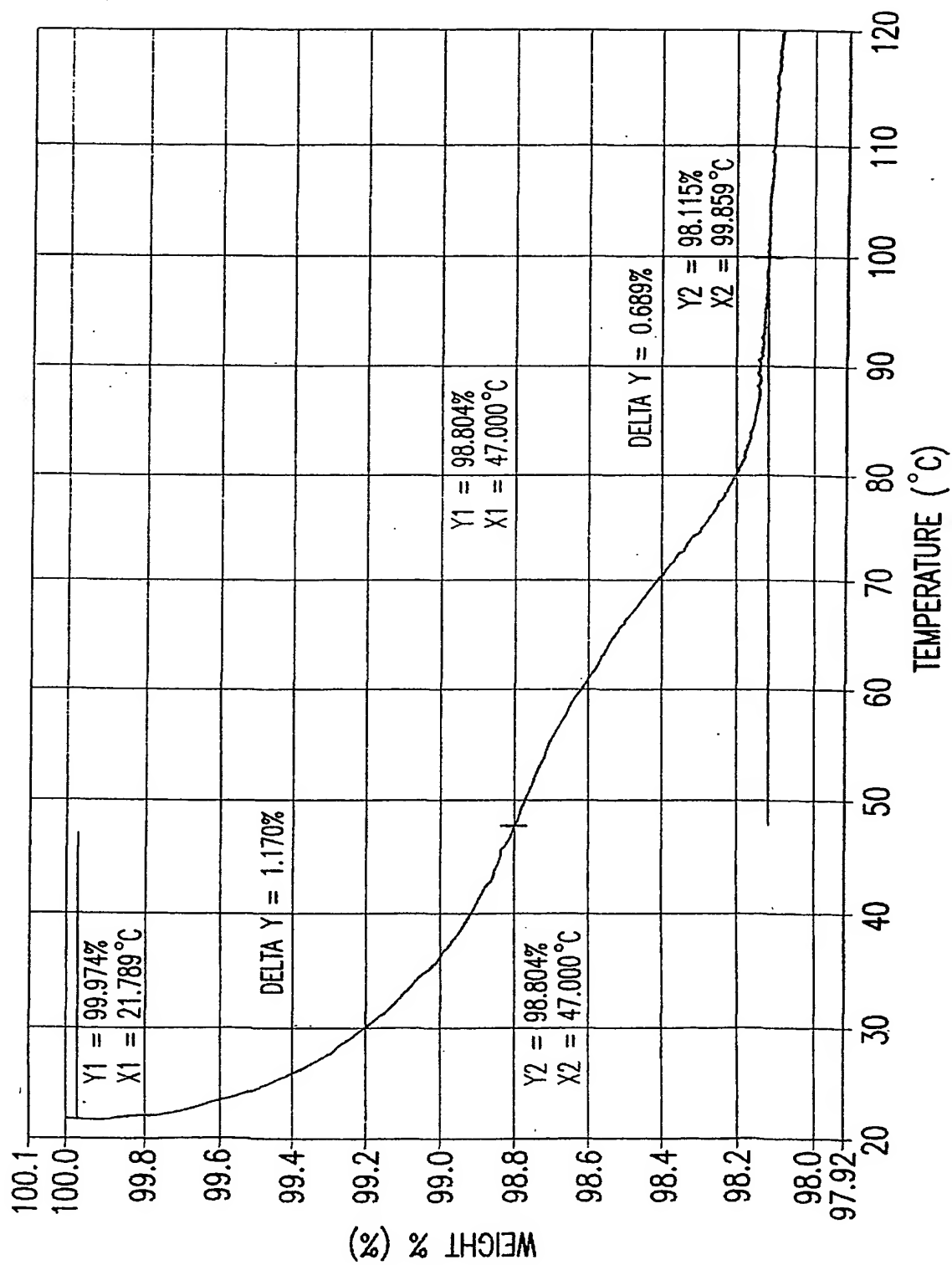


FIG. 20

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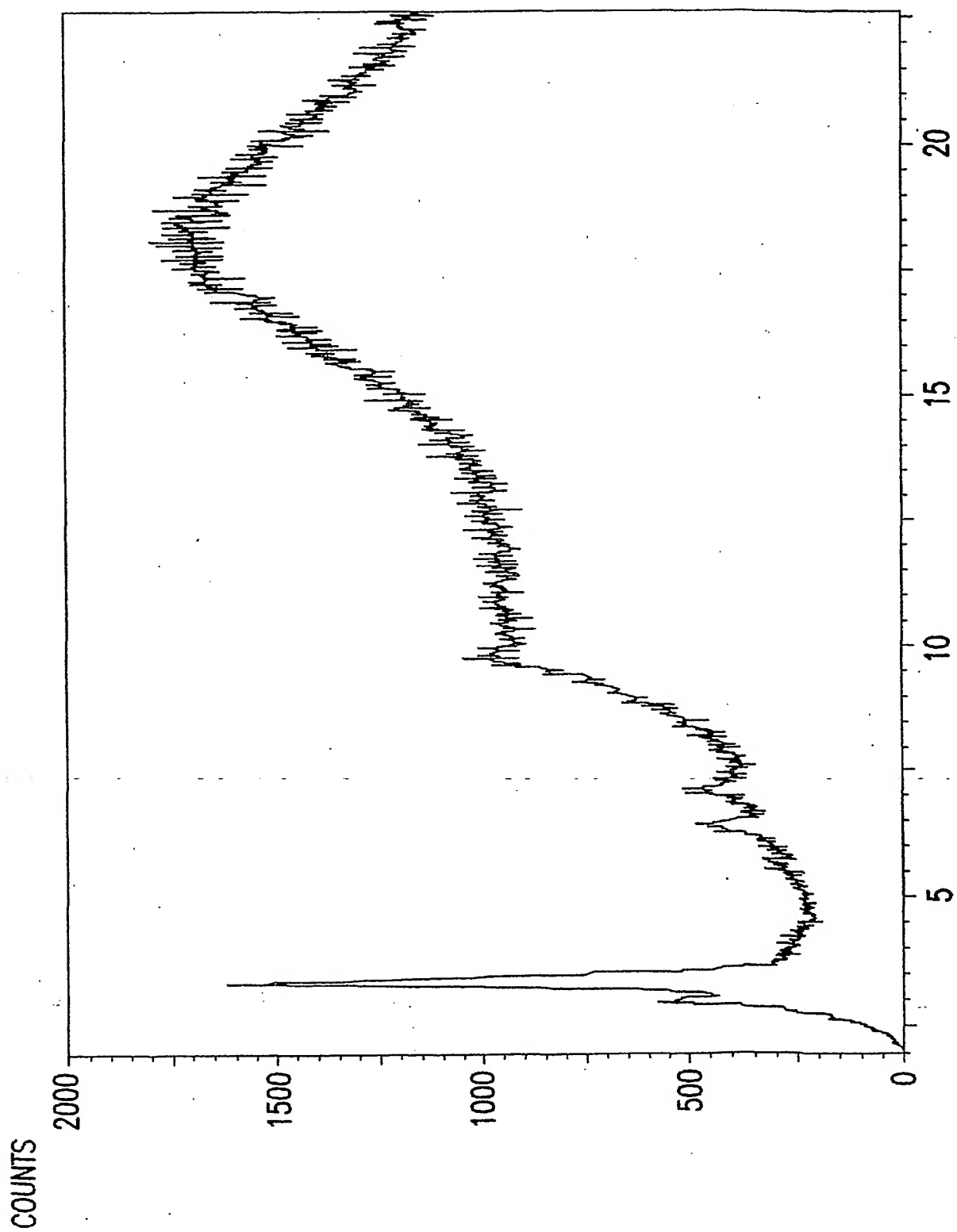
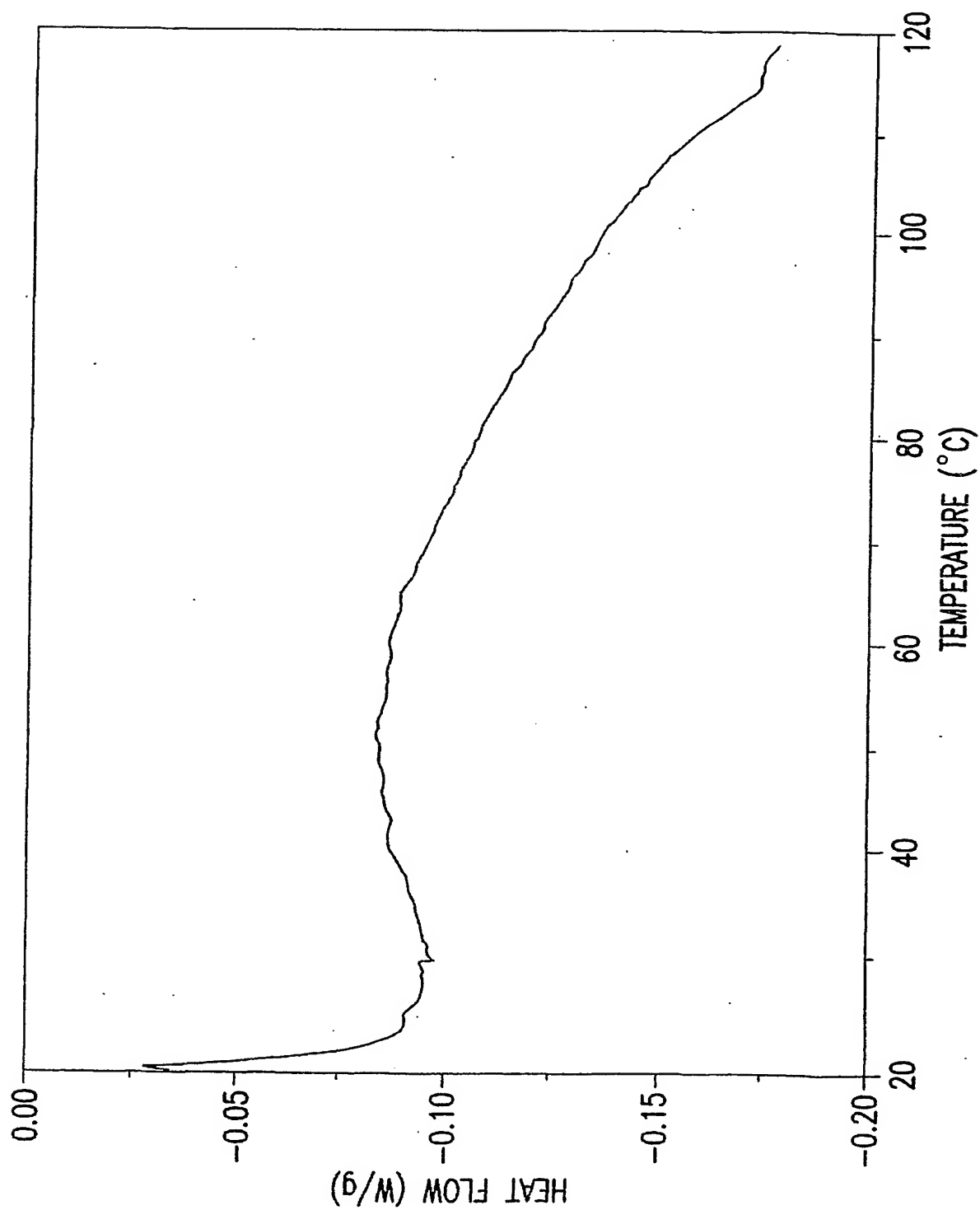


FIG. 21

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FIG. 22



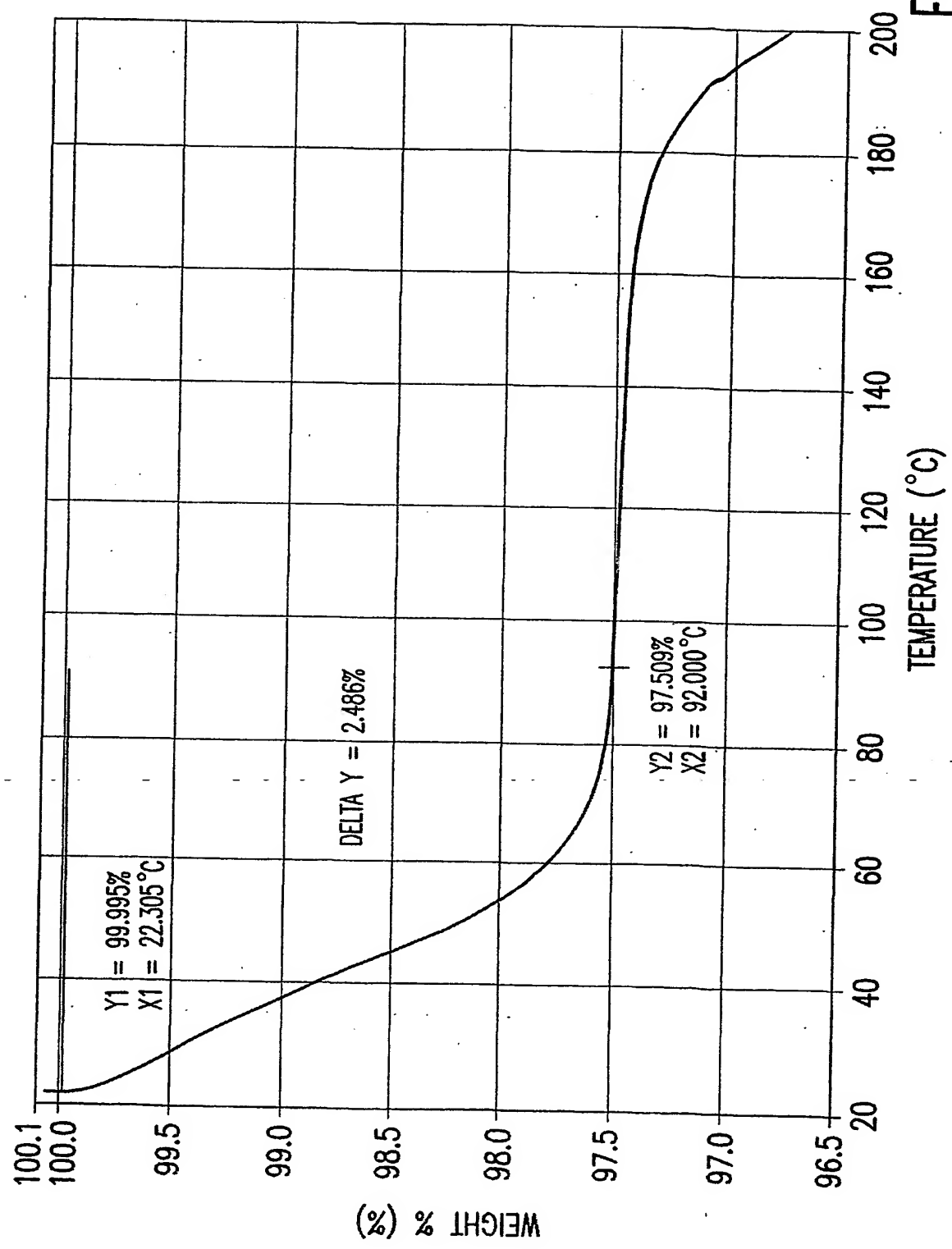


FIG. 23

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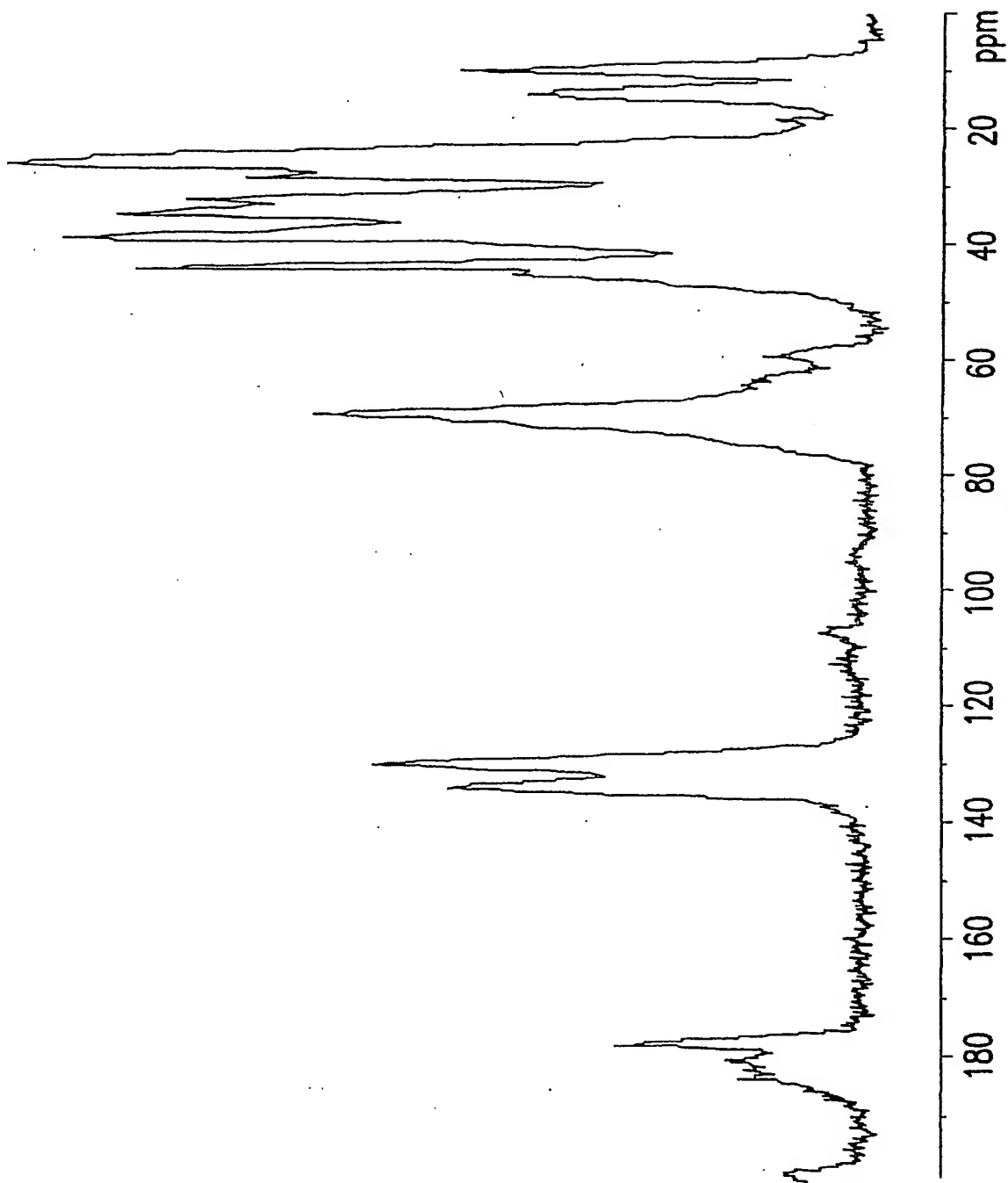


FIG. 24

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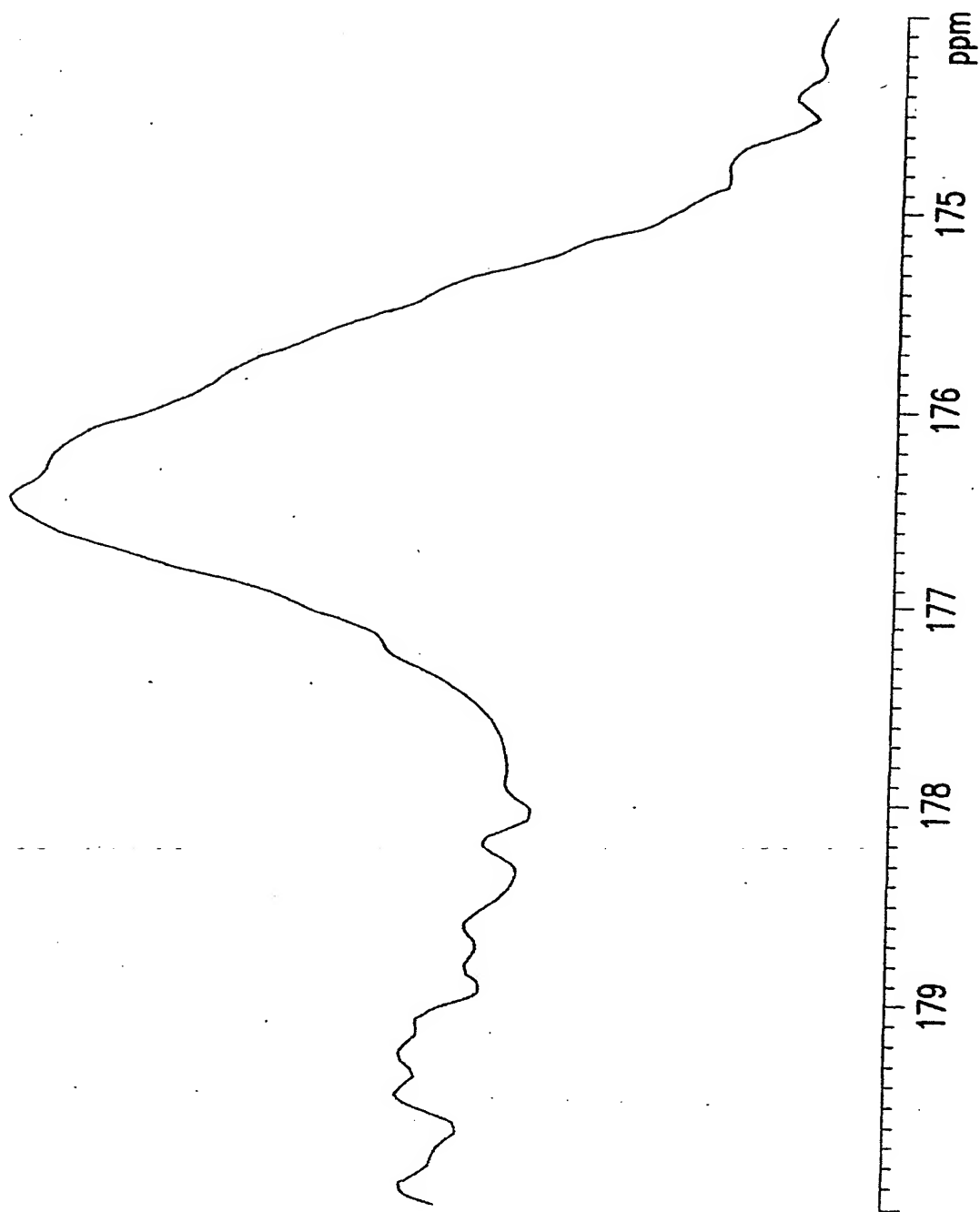


FIG. 25

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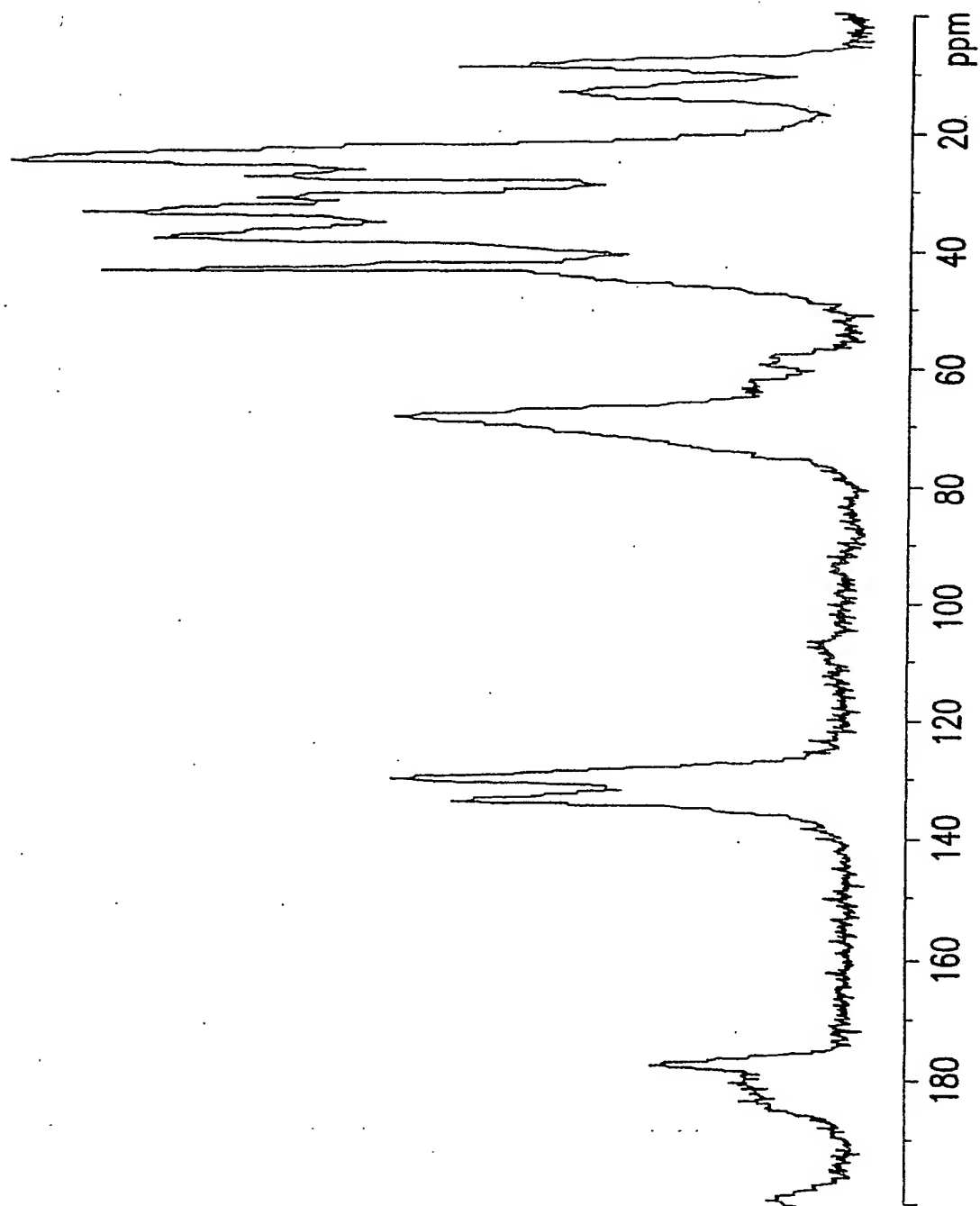


FIG. 26

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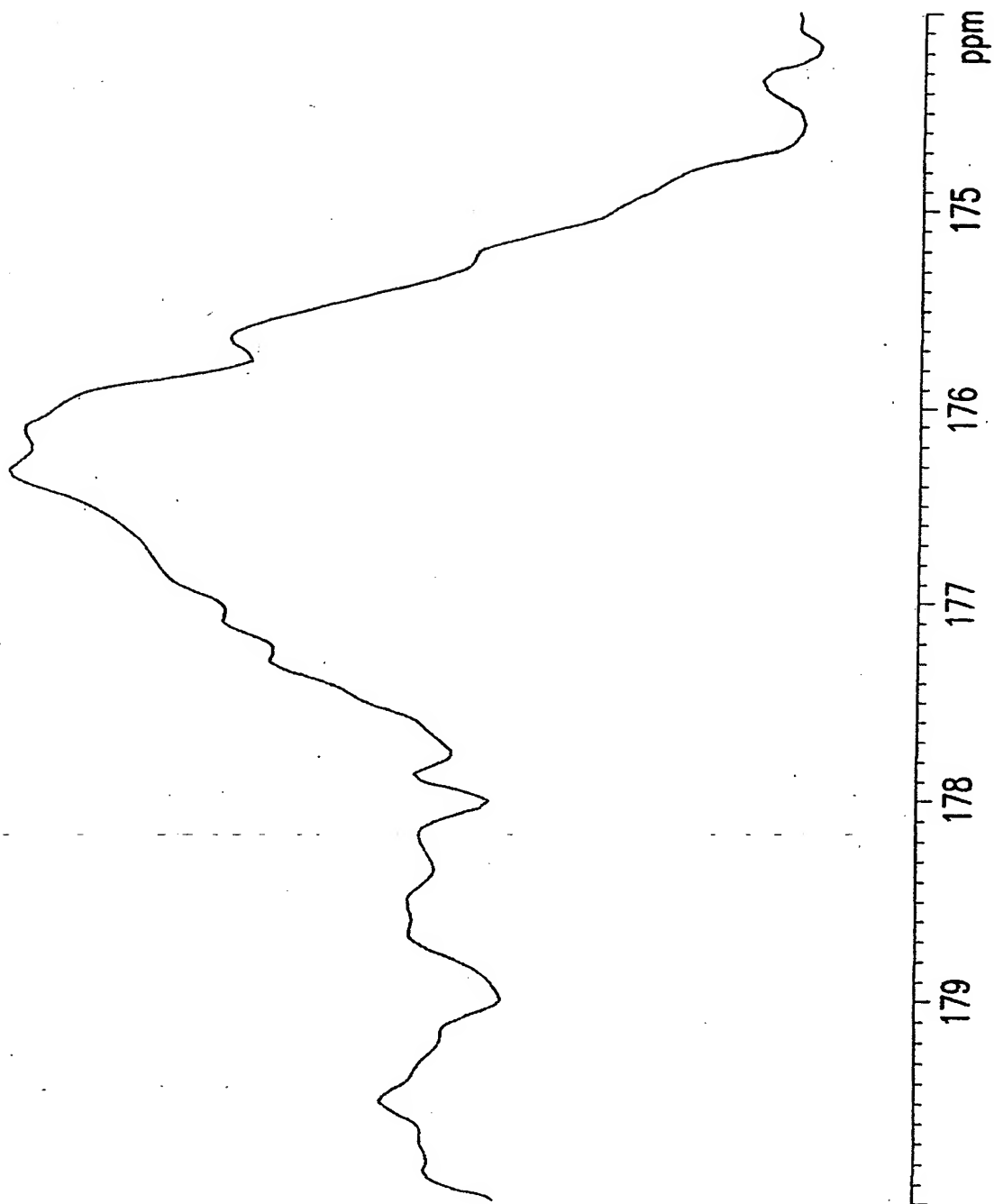


FIG. 27

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/27466

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : CO7C 69/30, 67/28; A61K 9/25, 31/22

U.S. CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 580/196; 549/275, 292

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00/53173 A1 (MERCK & CO., INC.) 14 September 2000, see entire reference.	1-160
X,P	WO 00/53566 A1 (MERCK & CO., INC.) 14 September 2000, see entire reference.	1-160
Y	US 5,223,415 A (CONDER et al) 29 June 1993, see examples and claims.	1-160
Y	GB 2055100 A (SANKYO COMPANY) 25 February 1981, see example 3.	1-160
Y	US 5,366,738 A (RORK et al) 22 November 1994, see entire reference.	87-90

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 NOVEMBER 2001

Date of mailing of the international search report

10 DEC 2001

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Telephone No. (703) 305-1235

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/27466

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL

560/196; 549/275, 292

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAPLUS

search terms: simvastatin, lovastatin, (ca or calcium) salt, crystal?

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